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THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

MARCH, 1930

ORIGINAL ARTICLES.

THE NEPHROPATHIC EFFECT IN MAN OF A DIET HIGH IN BEEF MUSCLE AND LIVER.*

By L. H. Newburgh,
PROFESSOR OF MEDICINE,
Mark Falcon-Lesses,
AND
Margaret W. Johnston,
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(From the Department of Internal Medicine, Medical School, University of Michigan)

In a recent publication[1] we showed that rats that lived on diets high in animal tissues (muscle and liver) gradually developed chronic sclerosing kidney disease. While it is generally believed that such results have a bearing on disease in man, any conclusions regarding him formed on the basis of such indirect evidence, are open to doubt. It is accordingly highly desirable to record the response to diets of this type in man himself.

We have had the opportunity of obtaining this information. The subject, a member of the laboratory staff, was an apparently normal man, aged thirty-two years.

During a preliminary period of thirty-five days he took a diet containing less than 100 gm. of protein daily, of which roughly 50 gm. were of animal origin.

During this time several careful physical examinations revealed no abnormalities. The blood pressure in the basal state was

* The expenses of this investigation were defrayed in part by a fund for the study of nutrition created by Mr. W. K. Kellogg of the Kellogg Corn Flake Company, Battle Creek, Michigan.

110 mm. systolic and 80 mm. diastolic. The nonprotein nitrogen of the blood was 31 mg. per cent. Three untimed fresh specimens of urine were tested for albumin by boiling and acidulating, with negative results; and for casts, of which a few were seen in one sample but none were noted in the two other specimens.

Addis[2] has shown that a few casts are usually present in the urine of normal persons and has emphasized the desirability of recording the number of casts voided in a unit of time as a criterion of the state of the kidneys. Three specimens were examined according to Addis' method. The subject saved all the urine from bedtime until 8 o'clock the next morning. None of the specimens contained enough albumin to be detectable by the usual clinical methods. The cast counts were respectively 49, 48 and 52 per hour. The urines were acid. Addis made 82 examinations of the night urines collected for twelve hours by 74 medical students. No casts were seen in 29 instances. The highest count gave 356 casts per hour and the average for the whole series was 87 casts per hour.

During the next six months, from April 10 to October 21, 1928, our subject received a diet specially prepared for him under the direction of Miss M. M. Harrington. Its composition according to the figures found in the standard food tables was as follows:

Protein	338 gm.
Fat	271 gm.
Carbohydrate	96 gm.

The calory value was 4177. Of the protein, 327 gm. were of animal origin and were contained in the following foods:

	Amount eaten.	Protein.
Fresh beef liver	about 400 gm.	80 gm.
Fresh veal round	about 300 gm.	60 gm.
Fresh beef tenderloin	about 700 gm.	164 gm.
Dried beef	about 100 gm.	33 gm.
		337 gm.

About one-quarter of the protein was contained in the liver.

In addition to these meats, the diet contained an adequate supply of vitamins and inorganic constituents in the form of butter, green vegetables and citrus fruits. Only 31 per cent of the calories of the diet were contained in the animal protein.

This diet caused no subjective disturbances. The retinæ remained normal. Of special interest is the fact that the blood pressure was unaffected by the diet.

The urine was examined twenty-five times during these six months. Albumin made its appearance for the first time after the subject had been on the diet for six weeks. Henceforth there was a gradual increase in the cloud caused by boiling and acidulating the filtered urine. However, the albuminuria was not great enough

to permit its measurement by the sulphosalicylic acid method[3] until the sixth month, when the subject was excreting 2 to 4 mg. of protein per hour.

The cast counts are contained in Table I. It will be seen that the counts during the first seven weeks (April 17 to June 5) were within the normal range based on Addis' experience. After that, the counts were definitely in the pathologic field. During the former period the highest count was 413 and the average of the seven counts was 216. Whereas during the final six weeks, the highest count was 3540 and the average of the ten counts was 1283, which is fifteen times the average obtained by Addis in controls.

TABLE I.—INCREASE IN CYLINDRURIA FROM HIGH MEAT DIET.

Date.	Casts per hour.	Date.	Casts per hour.
April 17	177	July 11	1109
April 19	84	July 11	1735
May 9	232	July 19	1856
May 17	104	September 9	400
May 23	413	September 12	1895
May 29	360	October 1,	0
June 5	142	October 8	952
June 12	1053	October 10	2048
June 19	1083	October 11	3540
June 26	601	October 17	0
June 29	1680	October 20	1500
July 10	974	October 22	2500

In addition, a change in the appearance of the casts took place as time went on. In the early weeks they were hyalin. Gradually more and more granular casts were seen. During the last weeks some of the casts were cellular and the hyalin variety was in the minority.

The urines were always acid, with a pH that was close to 5. The specific gravity varied from 1022 to 1027.

In order to make certain that the counts were not influenced by the desire of the observer, the following procedure was carried out during the last month. An associate prepared the urine from the subject and from himself and other controls, in the absence of the observer. The latter then made counts of specimens whose identity were unknown to him. In the urines of the controls he found 0, 20, 30, 197 and 213* casts per hour.

The high meat diet was discontinued on October 22. Thereafter the subject followed his own choice. He avoided meat and preferred carbohydrate. The urine examinations made after the change in diet are recorded in Table II. Recovery was complete in ten days.

The evidence reported makes it clear that a diet of which 31 per cent of the energy was contained in beef proteins caused a slowly

* From an individual who was suffering from acute rhinitis at the time.

increasing albuminuria and cylindruria* in our human subject. The continued excretion of these urinary abnormalities in noteworthy amounts indicates that the kidneys were being harmed by the diet.

TABLE II.—RECOVERY FROM HIGH MEAT DIET.

Date.	Albumin.	Casts.	Reaction.
October 24	Trace	1778	Acid
October 26	V.S.T.	980	Acid
October 27	S.P.T.	690	Acid
October 28	S.T.	140	Acid
November 2	0	0	Acid

When comparison is made between man and the white rat it must be remembered that the life span of the former is twenty times that of the latter and, therefore, six months in the life of a man corresponds to less than two weeks in that of the rat.

We have fed a group of 7 rats a diet 33 per cent of whose calories were contained in the proteins of beef muscle. The urines were examined for the first time when the animals had been taking this diet for more than one month. There was no increase over the usual trivial albuminuria found in normal rats. No casts were seen in 6 of the specimens. The seventh contained a few. Our experience with a similar type of diet, except that beef liver replaced the beef muscle, was the same.

A diet capable of producing a pathologic urine in a man was without detectable effect on the urine of the white rat. The kidneys of a man appear to be more easily injured than are those of the white rat by diets high in animal tissues.

TABLE III.—TOTAL URINE NITROGEN AND SOME OF ITS FRACTIONS FOR TWENTY-FOUR-HOUR PERIODS WHILE SUBJECT WAS EATING HIGH MEAT DIET.

Date.	Total N.	Uric acid.	Amino-acid N.	Creatinin.
July 24	57.0	1.16	0.48	2.54
July 25	57.5	1.84	0.43	2.37
July 26	60.5	1.91	0.46	2.80
August 13	54.2	1.77	0.43	2.98
August 14	51.5	2.46	0.37	2.72
August 15	55.0	1.99	0.44	2.70
October 15	45.3	1.54	0.44	2.19
October 18	54.9	1.97	0.57	2.50

Total N determined by Kjeldahl method.
Uric acid by Morris and McLeod method.
Amino acid N and creatinin by Folin methods.

There are in the literature a number of papers purporting to prove that an exclusive meat diet is not harmful to the kidneys of man. These reports, as a rule, deal with the life of the Eskimos

* In this connection, it is interesting to note that a chronic nephritic under our care at this time, with hypertension, nitrogen retention, retinitis and inability to raise the specific gravity of the urine above 1012, had an hourly excretion rate of only 5 mg. albumin and 5000 casts.

and are stated in such general terms that they are of questionable scientific value.

Recently, however, Thomas[4] succeeded in gathering some concrete information regarding 142 middle-aged Greenland Eskimos who had always lived on a carnivorous diet. He found albuminuria in 12 persons (8.5 per cent), excluding those that had pyuria; 9 (6 per cent) had hypertension. From these figures, he draws the surprising conclusion that "There is no unusual prevalence of vascular or renal disease" among these people. The examination of 16,662 men, policyholders of the Metropolitan Life Insurance Company,[5] revealed definite albuminuria in only 2.5 per cent of the group. The rate for men between the ages of forty-five to fifty-four years was 2.5 per cent; only 0.9 per cent showed a marked amount of albumin.

TABLE IV.—NITROGEN VALUES IN THE BLOOD DURING HIGH MEAT PERIOD.

Date.	N.P.N., mg. per cent.	Urea N., mg. per cent.	Uric acid, mg. per cent.	Amino-acid N., mg. per cent.
July 25	55.8	34.4	3.23	6.7
August 14	49.3	31.8	3.10	6.55
October 17	42.9	24.6	2.06	6.29
October 22	49.2	32.4	2.87	6.66
Twenty-four Hours After Return to Normal Diet.				
October 23	35.4	16.8	2.45	6.8

All determinations except uric acid by Folin methods: uric acid by Morris and McLeod method.

The blood samples were taken before breakfast in the morning. The subject had a meat sandwich at bedtime.

Furthermore, it should be pointed out that the response of the Eskimos to their diet does not necessarily furnish a measure of the effect of a similar diet upon men living in the temperate zone. The present Eskimos are presumably the product of adaptation, working through many generations, to the only possible food supply. The history of the white race has been different.

Recently, Lieb[6] has reported the failure to obtain evidence of renal impairment in the case of two arctic explorers who lived for twelve months on an "exclusive meat diet." The average composition of this diet was, in fact, such that 80 per cent of its energy was in the form of fat. Only 100 to 140 gm. of protein were eaten daily. To enhance the fat content of the meat, these subjects partook freely of suet and bone marrow. The persistent ketonuria[7] emphasizes that the chief characteristic of this diet was its abnormally high content in fat. It is important to draw a distinction between the connotation of the word "meat" as ordinarily understood, and that given it by these writers. Since the protein content of this diet is not far different from that habitually eaten by large classes of our population, one would scarcely expect to find marked evidence of kidney disease in the period of one year. Those who suspect that

the discovery of chronic nephritis in middle life is evidence that such a diet is harmful, believe that a great many years have been required to produce a recognizable injury. On the other hand, had these observers attempted to count the urinary casts, some evidence of abnormality might have been found.

In contrast to the negative character of the observations of Lieb and Tolstoi is the fact that our subject voided an abnormal urine within a few months after he had begun to live on a diet about half of which consisted of meat in the ordinary sense of the word.

Summary and Conclusions. A human subject, whose urine contained no albumin and less than the average number of casts found in normal men by Addis, lived for six months on a diet in which one-third of the calories were contained in beef proteins. As a result, he developed a significant albuminuria and a twenty-fold increase in casts.

Our earlier work has shown that it takes a longer time, relatively, to produce abnormal urine in the white rat by similar diets. Hence results obtained by means of the rat in this field are directly transferable to man.

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THE TREATMENT OF NONTROPICAL SPRUE WITH LIVER EXTRACT.

A Report of Two Cases.

By William B. Porter, M.D.,

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In a recent study[1] of 45 patients having a macrocytic type of anemia 2 patients were found to present clinical phenomena and laboratory data of such distinctive character that they were grouped as a specific disease entity. Their response to treatment

with liver feeding further emphasized their differential classification and it is noteworthy that the patients were replicas each of the other in their clinical state and course.

The cardinal characteristics of the disease have been an extreme degree of emaciation, severe anemia of the macrocytic type, chronic diarrhea, normal amounts of HCl in the gastric content, a complete absence of neurological phenomena, and rapid and consistent improvement following the feeding of adequate amounts of a potent liver extract.

We identify the condition as nontropical sprue in recognition of the fact that all of the symptoms and findings noted in our cases have been observed in sprue by other students of this disease.

In the treatment of the two cases here presented we have used a general hospital diet with the addition of liver extract E29* in amounts equivalent to 630 gm. of raw liver per diem.

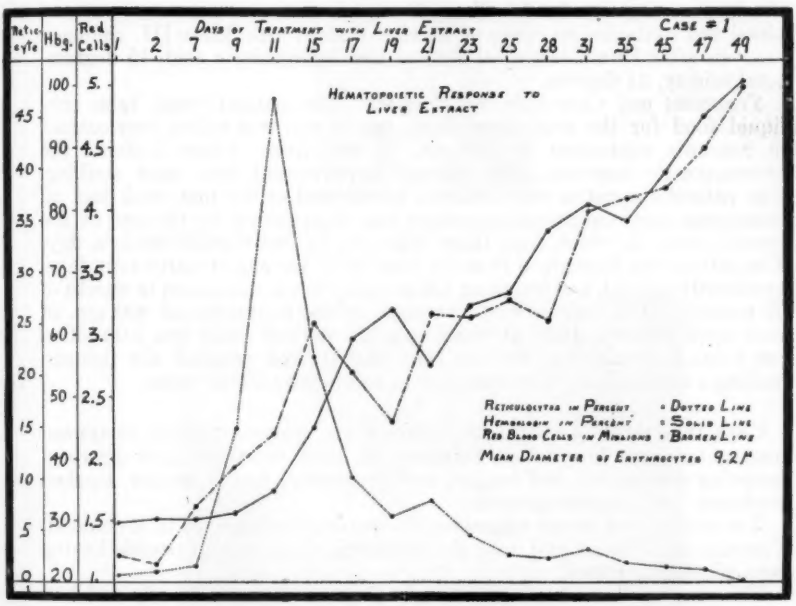
Reticulocyte
Hbg.
Red Cells
Days of Treatment with Liver Extract
Case #1
2 7 9 11 15 17 19 21 23 25 28 31 35 45 47 49
Hematopoietic Response to Liver Extract
Reticulocytes in Percent - Dotted Line
Hemoglobin in Percent - Solid Line
Red Blood Cells in Millions - Broken Line
Mean Diameter of Erythrocytes 9.2 μ

CHART I.

Case Reports. CASE I.—T. J., aged fifty-six years, an American negro, laborer, entered the hospital on August 20, 1928, complaining of recurring attacks of diarrhea accompanied with abdominal pain and rapid loss of weight, especially marked for the preceding seven weeks.

The past history is not suggestive, the patient having lived always in Virginia and until the beginning of the present trouble being always healthy and robust.

* Liver extract E 29 is an aqueous extract of liver developed by the Department of Medicine and Biochemistry of the Medical College of Virginia in collaboration with the Valentine Meat Juice Company, Richmond, Va., U. S. A.

The gastrointestinal symptoms began insidiously during the month of July, 1923. Since that time they have persisted with exacerbations consisting of diarrhea (8 to 10 stools per diem) anorexia, and rapid loss of weight. During remissions, 2 to 4 stools at night and 1 to 2 during the day represented the average degree of diarrhea. The stools were liquid and light in color. At the time the patient entered the hospital the number of stools was from 4 to 6 at night and from 2 to 3 during the day, watery in consistency but frothy and light in color. There was absolute anorexia.

Physical examination showed a markedly emaciated and undernourished male, manifestly quite ill. Height 5 feet 11 inches, weight 124 pounds. The tongue was pale with no atrophy of the papilla, but the tip and margins were raw and red. The abdomen was distended, tympanitic, and gave a doughy sensation when palpated. Proctoscopic examination was negative. No abnormal neurologic changes were elicited. Roentgenographic study of the gastrointestinal tract showed a moderate degree of megacolon. The blood count was: red blood cells, 1.1 million per c.mm.; hemoglobin, 29 per cent (Sahli); leukocytes, 4200 per c.mm.; polymorphonuclears, 52 per cent; lymphocytes, 48 per cent; reticulocytes, 0.2 per cent. Mean diameter of the erythrocytes was 9.5 microns. Wassermann reaction was negative. Stools were negative for Monilia psilosis, amœba, ova, parasites, pus and blood, but contained an excess of fat when stained with Sudan III. Stomach analysis after Ewald test meal showed free hydrochloric acid, 15 degrees, total acidity, 34 degrees.

Treatment and Course in the Hospital. The patient could take only liquid food for the first three days, but to this was added liver extract in amounts equivalent to 630 gm. of raw liver. Chart I shows the hematopoietic response. The clinical improvement was most striking. The patient's appetite was ravenous by the end of the first week and all distressing gastrointestinal symptoms had disappeared by the end of the second week, at which time there were one or two normal stools a day. The patient was discharged from the hospital at the end of thirty-four days, apparently normal, and weighing 156 pounds, which was a gain in weight of 32 pounds. The patient was continued on the equivalent of 400 gm. of liver until January, 1929, at which time the red-cell count was 5.9 million per c.mm.; hemoglobin, 110 per cent (Sahli), and weighed 178 pounds, making a total gain of 54 pounds in four and a half months' time.

Case II.—Mr. C. C., aged sixty-three years, white, an American tradesman, entered the hospital on February 19, 1929, complaining of diarrhea, recurring sore mouth and tongue, and progressive loss of weight, marked weakness and complete anorexia.

The past history is not suggestive, the patient having lived in Richmond, Virginia, all of his life and until the beginning of the present trouble having been physically robust.

The present illness began insidiously thirteen years previously and had continued with partial remissions since the onset. Chronic "indigestion" characterized by intestinal flatulence was a prominent symptom and he attributed the diarrhea to the gas which was marked at times. The type of stools had not been consistent in character. During the acute exacerbations there were 10 to 12 stools each twenty-four hours, 7 or 8 during the night and 3 or 4 during the day, watery in consistency, containing no blood or mucous, but gassy and irritating to the anus. In the remission, 2 to 3 stools in the early morning represented the average degree of diarrhea. These were large, soft, light in color and foamy. He had for two years attempted no work, had for a year lost much weight, and had been bedridden for two months previous to entering the hospital.

Physical examination revealed a markedly emaciated and undernourished

FIG. 1.—Appearance of Patient 2. Marked emaciation and lower abdominal distention. Weight 91 pounds.

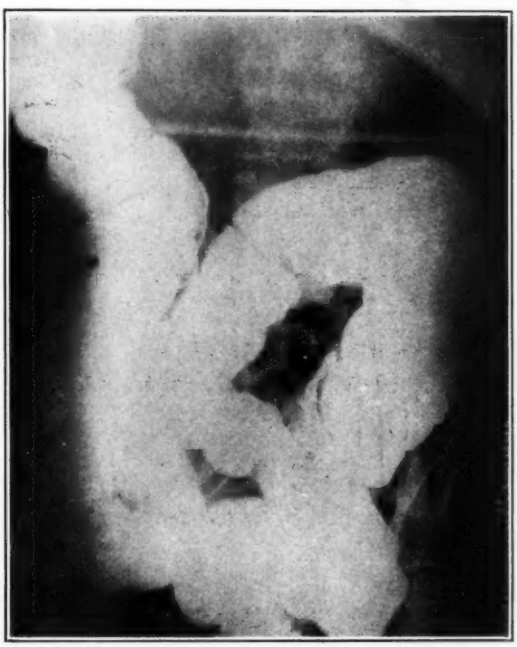

FIG. 2.—Megacolon in Case 2. Two thousand cubic centimeters of barium sulphate solution used as an enema.

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man, manifestly in the terminal stages of a severe illness. Height 5 feet 9 inches, weight 91 pounds. All teeth had been extracted three years previously and no artificial denture was used because of the recurring stomatitis. The tongue was pale with no atrophy of the papilla, but the tip and margins were raw and sensitive. The heart and lungs were essentially negative, but the peripheral arteries showed marked atheromatous changes of the Mönckeberg type, with a blood pressure of systolic 100 and diastolic 55. The abdomen was distended and tympanitic, but with no localized tenderness, and the size of the liver and spleen was apparently normal. There was edema of the feet and ankles extending to the middle of the leg. The neurologic examination was negative throughout. Proctoscopic examination was negative, and the roentgenographic study of the gastrointestinal tract was negative, except for a marked degree of visceroptosis and a moderate degree of megacolon (Figs. 1 and 2).

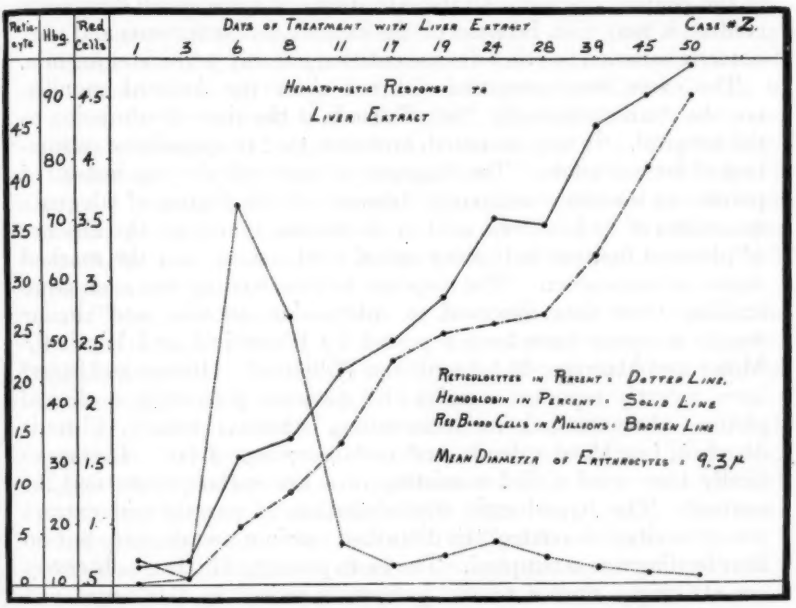
Reticulocyte
Hbg.
Red Cells
Days of Treatment with Liver Extract
Case #Z.
1 3 6 8 11 17 19 24 28 39 45 50
Hematopoietic Response to Liver Extract
Reticulocytes in Percent: Dotted Line.
Hemoglobin in Percent: Solid Line
Red Blood Cells in Millions: Broken Line
Mean Diameter of Erythrocytes: 9.3 μ

Chart II.

Laboratory Data. Hemoglobin, 13 per cent (Sahli); red blood cells 640,000 per c.mm.; white blood cells, 3800 per c.mm.; polymorphonuclear neutrophils, 12 per cent; eosinophils, 1 per cent; lymphocytes, 87 per cent; occasional normoblast; marked anisocytosis; poikilocytosis and slight polychromatophilia; reticulocytes, 0 per cent. Mean diameter of the erythrocytes was 9.3 microns. Wassermann reaction, negative. Stomach analysis after Ewald test meal showed free hydrochloric acid, 48 degrees, total acidity, 69 degrees. Stools were negative for blood, ova, parasites, Monilia psilosis and excess of fat with Sudan III. Blood calcium, 8.9 mg. per 100 cc.

Treatment and Course in the Hospital. The patient could take only liquid nourishment which was supplemented with liver extract in amounts equivalent to 630 gm. of raw liver. Chart II shows the hematopoietic response. The clinical improvement was most striking. Within five days

the patient's appetite was ravenous and he was taking a general diet. All distressing gastrointestinal symptoms, together with his stomatitis had disappeared by the twelfth day, and there were one or two normal stools a day. The patient was discharged from the hospital at the end of forty-nine days, weighing 127½ pounds—a gain of 36½ pounds, and apparently well. He was last seen on May 14, 1929, at which time his weight was 136 pounds. He stated that he felt well and was able to work as a shoemaker, eight hours a day.

Discussion. The diagnosis of sprue is still on an unsatisfactory basis. During the early stages of the disease it may be confused with a large group of heterogeneous intestinal disturbances; some of which may eventually develop a clinical picture characteristic of the genuine disease. In the late stages of sprue much diagnostic confusion may rise, because of the existence of symptoms and phenomena common to other disease entities, notably pernicious anemia.

The cases here presented did not show the Ashford monilia, nor the characteristically "fatty" stools at the time of admission to the hospital. It may be noted, however, that no quantitive estimation of fat was made. The diagnosis of nontropical sprue instead of pernicious anemia was favored because of the finding of adequate quantities of hydrochloric acid in the stomach content, the absence of physical findings indicating spinal cord lesions, and the marked degree of emaciation. The response to liver feeding was even more striking than that observed in Addisonian anemia, and similar results in sprue have been reported by Bloomfield and Wychoff,[2] Minot and Murphy,[3,4,5] Ashford[6] and Williams.[7] Holmes and Starr[8] have recently reported a series of 5 patients presenting a clinical picture characterized by emaciation, anemia, tetany, chronic diarrhea, low blood calcium and malabsorption of fat. Therapeutically they used a diet consisting of a low carbohydrate and fat content. The hypodermic administration of parathyroid extract was prescribed to control the disturbed calcium metabolism, but no liver feeding was attempted. The cases presented by these observers are strikingly similar to the patients reported in this series and probably represent the same clinical entity.

The nature of the anemia occurring in sprue has for many years been a topic for much discussion. Smith,[9] and Baumgartner and Smith[10] have expressed themselves as believing that the anemia of sprue is aplastic. Reed and Ash[11] in discussing "atypical sprue" mention a group of 11 cases observed in the Philippines with advanced anemias "invariably aplastic in type and progressive in spite of all treatment." Ashford,[6] commenting on the results in 14 patients with tropical sprue treated with liver extract noted that the 10 patients having an anemia of the "primary type" all improved, but the 4 patients having a "secondary type" of anemia showed not the slightest response to liver extract. The hematopoietic response in our patients having nontropical sprue and in the

cases of sprue reported by other American observers using whole liver or liver extracts would indicate that the anemia is neither aplastic nor secondary, but dependent upon a disturbance of bone marrow physiology similar to that found in Addisonian anemia.

The finding of adequate amounts of hydrochloric acid in the stomach contents of patients who have blood pictures of an advanced macrocytic anemia, but without phenomena indicating a myelitic process, strongly suggests that the megaloblastic anemias may be dependent upon an independent factor, and the absence of neurologic pathology in the cases here reported would indicate that the presence of normal gastric enzymes had functioned as a prophylactic agent, protecting the organism against the development of neurotoxins; a complication so consistently found in pernicious anemia. One cannot escape the conviction that this is a useful working hypothesis and that adequate amounts of hydrochloric acid should be administered routinely in the treatment of patients having a primary type of anemia and achylia gastrica regardless of how completely the blood has been restored to normalcy with liver feeding.

Summary. 1. Two patients presenting clinical characteristics of sprue with marked degrees of macrocytic anemia but without monilia psilosis in the stools or on the mucous membranes of the mouth, have been treated with liver extract with prompt relief of all symptoms of the disease.

2. The hematopoietic response to liver indicates that the anemia was neither secondary nor aplastic, but associated with a megaloblastic hyperplasia of the bone marrow and was fundamentally of the same type as the anemia of Addison.

3. The prompt relief of intestinal disturbance by the use of that substance contained in mammalian liver is most striking and suggests that the anemia and its associated disturbance of intestinal physiology may be essentially a deficiency disease; and that nontropical sprue is not a moniliasis of the digestive tract.

4. The notable absence of all neurologic phenomena in patients having advanced degrees of macrocytic anemia with normal amounts of hydrochloric acid in the gastric content suggests that the spinal cord changes in pernicious anemia are definitely related to the achylia gastrica found in that disease.

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THE RELATION OF CHOLESTEROL, LECITHIN PHOSPHORUS AND FATTY ACIDS TO THE REMISSION OF PERNICIOUS ANEMIA.

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In the opinion of many investigators, disordered cholesterol metabolism is an important aspect of the disease pernicious anemia and of the so-called hemolytic anemias. This opinion has been fostered mainly by two facts, namely: that cholesterol is an anti-hemolytic agent[1–6] and that usually cholesterol is reduced in anemias of this type and consequently this lack may play a rôle in the causation of these anemias.[7] This conviction of the importance of cholesterol in pernicious anemia is reflected in the literature where a number of reports are found describing its therapeutic use, with results varying from ineffectiveness to considerable improvement.[8–15] MacAdam and Shiskin[16] point out that when the patients improve there is conclusive evidence of increased cholesterol in the plasma and decreased hemolytic activity. This has subsequently been confirmed by others.[17–19] The opinion of Bloor[20] that the low values for cholesterol in the plasma of pernicious anemia patients are not without significance in view of the part cholesterol is said to play in protecting corpuscles from the action of hemolytic agents, has been voiced by many investigators[17, 21–25] while others[26–28] have advanced the opinion that the general disturbance of the lipoid metabolism of the body is the primary cause of the disease. McNee[29] however, refuted the idea that the low cholesterol in pernicious

anemia patients is due to the utilization of this substance as an antihemolytic agent.

A relation between red blood cell destruction and the amounts of lipoids in the blood was suggested by Erben in 1902.[30] From studies concerning the lipoid metabolism in chlorosis he concluded that blood destruction does not take place in this disease because the lipoids in the blood were not increased, and, in fact, he found them decreased. He thought that if there was a great destruction of red blood cells, the lipoids would be increased, and this would be so much more marked in chlorosis as the fat metabolism is impaired.

Experimentally it has been shown that destruction of erythrocytes *in vivo* caused an increase of cholesterol both in the blood, bile and feces.[31–34] Bodansky,[35] however, obtained a variable result in dogs. In contrast to the experimental work stand the human anemias of the so-called hemolytic type, many of which show a decrease of cholesterol and lecithin in the blood. The picture is still further confused by the fact that low cholesterol values are found in other types of anemia in which increased blood destruction cannot be demonstrated.

This has led some observers to conclude that the number of red blood cells, that is, the anemia, is directly related to the level of the cholesterol. This opinion has been voiced by Schnabel[36] and Strathmann-Herweg,[37] who concluded that the anemia itself, not a hypothetical toxin causing the anemia, must be responsible for the low cholesterol in the blood. Bloor[38] suggested that inasmuch as there is considerable evidence to show that the red blood cells participate in the fat metabolism, the low values of lecithin may be regarded as due to deficient fat assimilation from the lack of sufficient corpuscles to bring about the change.[39] The numerical lack of red blood cells would furnish a simple explanation of the decrease of the lipoids in the blood in a certain number of cases of anemia and would include all anemias due to any cause.

It is well known that the cholesterol in the blood increases in pernicious anemia when the patient improves. Wesselow[40] and Beck[41] found a rough parallelism between the increase of erythrocytes and the cholesterol in the blood, the highest red blood cell count corresponding with the highest cholesterol values. However, an analysis of the relation of the concentration of red blood cells and hemoglobin to the amount of cholesterol in the blood revealed that no correlation existed.[16, 17, 42] An analysis of 172 cases of pernicious anemia recorded in the literature[43] indicates that very variable results have been obtained even after allowance has been made for variations dependent upon technical methods. This variableness has been commented upon by Köhn.[17] Many reports are inadequate. A great number of investigators report only one determination, often without recording count of the corpuscles or any other description of the stage of the disease. Thus in 120 out of 172 cases only one

cholesterol determination was made, 69 of which were accompanied with no data for red blood cells and hemoglobin.

The initial values in the 172 cases collected from the literature according to the standard of normal set by the respective authors were above normal in 18, normal in 47, and below normal in 107 or 62.2 per cent. Of the 101 cases, in which red blood cells are recorded, 21 cases had below 1 million per c.mm., 47 had between 1 and 2 millions per c.mm., and 21 between 2 and 3 millions per c.mm., while 11 had over 3 million red blood cells per c.mm. In the group with less than 1 million corpuscles per c.mm., 71.4 per cent had subnormal values for cholesterol, while in the group with between 1 and 2 million erythrocytes per c.mm., 61.7 per cent, and in the group with between 2 and 3 millions, 45.4 per cent had cholesterol values below normal. Thus only 54.7 per cent with a reduction of red blood cells and hemoglobin below 50 per cent of normal showed subnormal values for the blood cholesterol, while the remainder had normal or high values.

In view of the variableness of the results reported and the confusing picture obtained, it was thought worth while to restudy the relation of cholesterol, lecithin, and fatty acids in the blood plasma to the remission of pernicious anemia, and the changes brought about by various treatments calling forth a remission, especially in view of the greater control over the various phases of the disease that is offered by recent developments in therapy.

Procedure and Methods. Determinations of cholesterol, lecithin phosphorus and fatty acids in the plasma of 36 individuals have been made. Of these, 26 were undoubted and 8 doubtful cases of pernicious anemia, and 2 were healthy young males.

The examinations were carried out under as uniform conditions as possible so as to obtain comparative results. The blood as a rule was obtained at the same time every second day, in most instances over periods of weeks and in some instances during several months. The cholesterol and fatty acids were determined by Bloor's saponification method[44] and the lecithin phosphorus according to the method of Whitehorn,[45] both methods giving consistent values in duplicate. Brownish discolorations in the cholesterol determinations were obtained only exceptionally, and it was seldom marked enough to interfere with the readings. Citrated plasma was used as it has been shown[39] that the corpuscles in anemia as well as in other conditions tend to preserve a constant lipoid composition, abnormalities being found mainly in the plasma.

The 26 cases of undoubted pernicious anemia have been divided for convenience in 3 groups, depending upon the severity of the anemia. These three groups include: (1) 6 patients with less than 1 million red blood cells per c.mm.; (2) 13 with between 1 and 2 million red blood cells per c.mm., and (3) 8 with above 2 million red blood cells per c.mm. This arbitrary division was made because

as a rule, the lower the red blood cell count the greater the rise of the reticulocytes in the peripheral blood.[46] It seemed of interest to attempt to correlate the reticulocyte rise to the lipoids of the blood.

The remissions of these pernicious anemia patients were called forth by various dietary procedures in conjunction with work done by Castle,[47] on the relation of achylia gastrica to the etiology of pernicious anemia, as well as by the addition of liver, liver extracts and kidney to the ordinary diet. A preliminary report of the work has been made.[48]

GROUP 1. Of the 6 cases with less than 1 million red blood cells per c.mm., all showed low values for both cholesterol and lecithin, and 3 had even less than 50 per cent below normal.

Of these 6 cases 4 had a rapid remission, 1 died, and 1 remained in a stationary condition for about four months. The remissions were

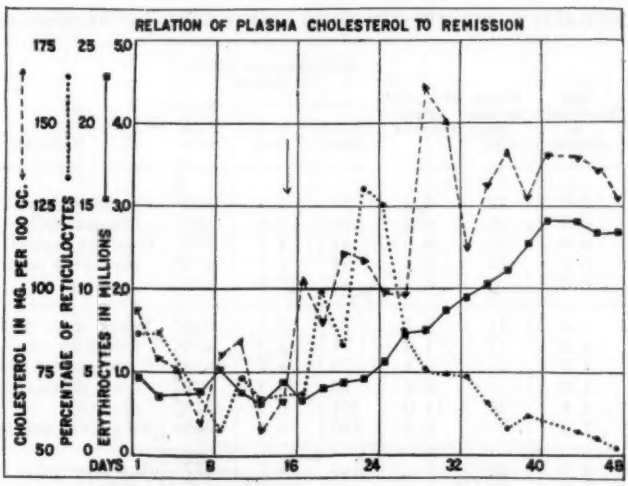

CHART I.—A case of pernicious anemia with erythrocytes below 1 million per c.mm. On the fifteenth day (note arrow) the reaction of the meat preparation was changed from pH 3 to 5.5.

called forth by feeding material rich in the active principle effective in pernicious anemia. The patient who died did so before proper treatment could be instituted, and the one whose condition remained stationary received no liver therapy.

The course of one of these cases is illustrated in Chart I. The diet was kept constant for the entire period, except that on the eighteenth day the pH of the meat that was fed after partial digestion with normal gastric juice was changed from 3 to 5.5. The chart shows that concomitant with the rise of the reticulocytes indicating the onset of remission, there was a sudden rise in the blood cholesterol, followed by small variations at the new level for about twelve days; then a secondary rise to a normal level took place which was main-

tained, as the reticulocytes gradually fell to normal values. The curve of the lecithin phosphorus followed the same general trend as that for the cholesterol, except that the secondary rise was not so marked. During the entire period the fatty acids varied within normal limits. Before the remission the fatty acid values were between 405 and 467 mg. per 100 cc. of plasma while after the remission commenced they varied from 384 to 491 mg. per 100 cc.

A second case with less than 1 million red blood cells per c.mm. during a nine-day control period was fed with an inert meat preparation. The course taken by the red blood cells, reticulocytes, cholesterol and lecithin phosphorus is illustrated in Table I. This table

TABLE I.—A PERNICIOUS ANEMIA PATIENT SHOWING RISE AFTER TRANSFUSION OF THE RED BLOOD CELLS WITHOUT INCREASE IN THE LIPOIDS. INCREASE OF CHOLESTEROL AND LECITHIN OCCURRED CONCOMITANT WITH THE ONSET OF REMISSION.

Days.	Red blood cells in millions.	Hemoglobin, per cent.	Reticulocytes, per cent.	Milligrams per 100 cc. of plasma.			Remarks.
				Cholesterol.	Lecithin.	Fatty acids.	
1	0.6	22	0.2	53	4.1	425	Predigested meat, 250–300 gm. daily.
3	0.8	21	0.5	86	5.0	431	
5	0.6	19	0.6	91	4.7	469	Gain of weight during period, 3½ pounds.
7	0.7	14	0.2	87	4.7	479	
9	0.6	15	0.1	48	3.9	419	
11	1.5	21	0.7	68	3.1	389	Transfusion, 500 cc. citrated blood.
13	1.2	17	1.0	71	4.2	426	
15	1.3	..	0.4	73	4.7	422	Experimental liver extract of moderate potency.
17	1.5	..	6.0	79	4.4	437	
19	1.4	25	14.0	101	6.2	513	
21	1.6	..	3.3	110	6.5	586	No gain in weight.
25	2.0	38	....	160	8.7	437	Raw liver pulp, 200 gm. daily.
27	1.8	38	....	151	6.1	498	
29	2.0	..	....	142	7.8	511	Gain of weight, 15 lbs. in one month.
31	2.8	51	....	142	8.1	465	
33	2.6	..	....	143	8.4	447	
38	3.6	53	....	150	7.9	476	

shows that the red blood cells remained about 700,000 per c.mm., while the cholesterol varied from 48 to 91 mg. per 100 cc. of plasma, and the lecithin phosphorus from 3.9 to 5 mg., the lowest values being obtained on the ninth day when the patient was in a critical condition. A transfusion of 500 cc. of citrated blood was given and on the same day the patient was placed on a daily dose of potent liver extract. Following the transfusion the red blood cells rose from 600,000 to 1,500,000 per c.mm., without any appreciable rise of cholesterol or lecithin. On the sixth day after transfusion and the commencement of the administration of the liver extract,

remission set in as indicated by the rise of the reticulocytes, and the cholesterol had increased on the eighth day by about 40 per cent. This new level was maintained for six days, and then suddenly increased to normal values. Changes in the amount of lecithin phosphorus accompanied those of the cholesterol while the fatty acids during the entire period remained normal. The secondary increase of the cholesterol in this case was concomitant with a change from liver extract to raw liver. However, this increase of cholesterol was not due to cholesterol in the liver but to the administration of adequate amounts of the principle effective in pernicious anemia.

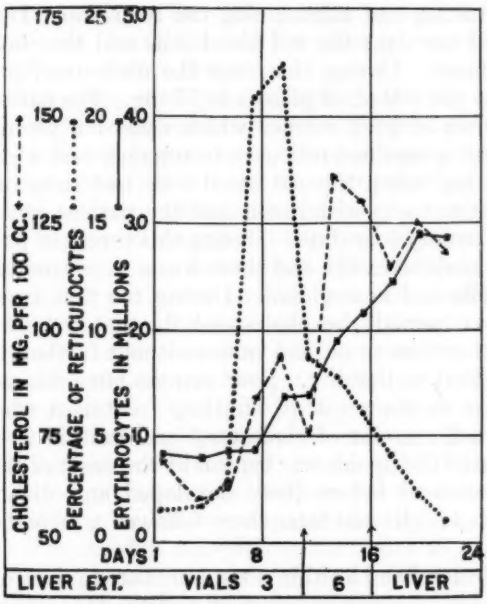

CHART II.—The effect of liver extract upon the plasma cholesterol in a case of pernicious anemia.

Note the moderate increase of the cholesterol with small doses of liver extract, the establishment of a normal level with larger doses, and the maintenance of the level when 240 gm. of broiled liver were fed daily. Each vial represents 100 gm. of liver of Liver Extract 343, N.N.R.

That liver feeding will not influence the content of the cholesterol and lecithin phosphorus in the plasma if unrelated to the remission as such, is illustrated in Chart II. This patient had 850,000 red blood cells per c.mm. before treatment. Liver Extract 343 (N.N.R.) derived from 300 gm. of liver was given daily for ten days. On the sixth day, reticulocytes commenced to rise. The cholesterol before remission varied between 60 and 70 mg. per 100 cc., then during the reticulocyte rise between 75 and 94 mg. On the

eleventh day the daily dose of liver extract was changed from that derived from 300 gm. to that derived from 600 gm. Two days later the cholesterol was 135 mg. per 100 cc., and remained at this normal level, without any further increase, when the patient was put on comparable amounts of whole liver. This indicates that a close relationship exists between the dosage of the principle effective in pernicious anemia and the rise of cholesterol in the plasma. The values of the lecithin phosphorus in this patient were not exceedingly low and the rise consequently not marked.

A fourth patient illustrates the influence on the lipoids of a remission which is not maintained, because of the withdrawal of the material initiating and maintaining the remission. During a control period of ten days the red blood cells and the cholesterol and lecithin declined. During this time the cholesterol gradually fell from 139 mg. per 100 cc. of plasma to 77 mg. The patient then was fed large doses of liver extract which caused a prompt onset of remission with a maximal reticulocyte response and a rise of cholesterol to 111 mg. when the red blood cells had risen only slightly. The liver extract was withdrawn and the patient put on a meat-free diet for twenty-four days. During this time, the patient gained weight (9 pounds) steadily and there was a slow gradual rise of the red blood cells and hemoglobin. During the first twenty days of this meat-free period the cholesterol fluctuated between 89 and 139 mg., it then rose to normal values without further change when steak was added to the diet. Four months later the patient had a severe relapse as the result of omitting treatment when again he showed a small amount of cholesterol and lecithin in the plasma. The response of the lipoids was typical at the onset of the remission, becoming increased before there developed any distinct increase of the red blood cells and later there followed a secondary rise to a normal level.

If the cholesterol and lecithin phosphorus are to show any increase, the change occurring in the organism and the hematopoietic organs which is designated as a remission must be real and lead to improvement. This is illustrated by the fifth case, with less than 1 million red blood cells per c.mm., which was followed for a period of four and a half months. This patient's blood count was increased from 900,000 to 1,800,000 per c.mm. by a transfusion of blood without any change in the lipoids of the blood. A remission due to feeding suboptimal doses of a material rich in the active principle effective in pernicious anemia with a reticulocyte count of only 16.9 per cent was frustrated by a change to an inert preparation and the red blood cell count remained stationary. With optimal doses at this low level of red blood cells, the reticulocyte response ought to have been about 35 per cent. The determinations made every second day were, respectively, 42, 32, 52, 73, 89 mg. per 100 cc. of plasma and the lecithin phosphorus rose from an average of 8 to 10 mg. per

100 cc. of plasma, without change in the level of fatty acids. This attempt of remission was not sustained and was not reflected in the increase of the erythrocytes and hemoglobin, illustrating convincingly that the cholesterol rises in proportion to the dose. This patient served for a long time to test materials and this was reflected in the cholesterol, which remained low during a four and a half month period, the values obtained varying between 32 to 98 mg. per 100 cc. of plasma. The lecithin phosphorus reached normal values at the time of the rise of the reticulocytes, then fluctuated between normal and values 50 per cent below normal.

In the sixth case, with a sudden fatal termination probably due to cerebral hemorrhage, the cholesterol remained low during one week's observation, while the lecithin phosphorus rose from 5.4 to 9.1 mg. per 100 cc. before death.

From these 6 cases, it may be concluded that the low values for cholesterol found in relapse change in an upward direction suddenly at the time remission begins, irrespective of the measures taken to establish a remission. The increase does not precede the reticulocyte rise but as a rule is concomitant with it, and occurs before any significant increase in the concentration of the red blood cells and hemoglobin. As far as can be determined from the data at hand the increase of cholesterol is not gradual but rises rapidly to a level somewhat below normal, remains there for a short interval, then shows a secondary rise to normal or to somewhat above normal. Transfusion of blood does not have any influence on the cholesterol content of the patient's blood. To obtain an increase of cholesterol and maintain the level a complete remission is usually necessary. A change in the form of effective therapy, as from liver extract to whole liver, causes no increase in cholesterol, indicating that the food as such has little or no influence in establishing the normal cholesterol level. The lecithin phosphorus fluctuates as a rule with the cholesterol although this was not observed in all cases. Practically normal values of the lecithin phosphorus may be observed with low values for cholesterol. The fatty acids in these patients varied within normal limits and no change in these constituents was seen at the onset of the remission.

GROUP 2. Twelve cases comprise this group of patients entering the hospital with a red blood cell count between 1 and 2 millions per c.mm. Eleven showed both a low cholesterol and lecithin content of the blood, while one had normal values. Five were treated with liver extract, and all promptly remitted. It is of interest to note that the case with the greatest concentration of reticulocytes at the peak of their rise had the cholesterol increase more promptly and of greater magnitude than the others. These cases illustrated the maintenance of the low level of cholesterol for long periods when inert preparations of meat or liver extract were tested and the rapid rise in remissions produced by adequate amounts of

potent material. In those cases fed suboptimal amounts of potent material the cholesterol tended to rise less abruptly and seemed somewhat delayed in exhibiting the secondary rise to a normal level.

This state of affairs is illustrated in Table II.

TABLE II.—A PERNICIOUS ANEMIA PATIENT WITH A FEEBLE RESPONSE DUE TO INADEQUATE LIVER THERAPY. THE CHOLESTEROL RISE IS LESS ABRUPT AND SOMEWHAT DELAYED IN REACHING A NORMAL LEVEL.

Days.	Red blood cells in millions.	Hemoglobin, per cent.	Reticulocytes, per cent.	Milligrams per 100 cc. of plasma.			Remarks.
				Cholesterol.	Lecithin.	Fatty acids.	
1	1.8	31	0.6	67	5.2	476	
5	1.3	26	....	65	8.2	437	Experimental liver extract without potency.
7	1.7	45	0.8	92	7.7	428	
9	1.6	..	4.0	98	9.3	395	
11	1.6	34	2.0	73	9.8	416	
13	1.6	..	2.4	93	8.7	451	
15	1.7	42	2.8	84	8.8	441	
17	1.6	40	1.1	107	6.4	421	Liver Extract 343 N.N.R. derived from 300 gm. of liver.
19	1.7	45	3.4	103	8.4	469	
21	1.7	42	6.4	123	10.8	386	
22	...	..	13.2				
23	1.8	42	....	120	10.7	355	
24	...	..	10.9				
25	2.0	51	5.6	118	9.4	400	
27	2.5	67	....	97	9.7	405	
29	2.5	76	....	103	9.8	416	
31	2.5	64	....	107	8.3	447	
35	2.8	79	....	144	11.1	438	
38	3.1	72	....	129	9.4	415	
42	3.2	74	....	136	9.5	441	Raw liver pulp, 250 gm. daily.
52	3.7	80	....	137	10.3	454	

Two of the patients deserve individual comments. A woman, aged seventy-one years, with 1.1 million erythrocytes per c.mm. and with 88 mg. of cholesterol and 3.7 mg. of lecithin phosphorus per 100 cc. of plasma was fed daily special prepared predigested meat. Determinations of the lipoids were done daily. For the first week, the red blood cells varied between 1 and 1.2 millions per c.mm., cholesterol between 77 and 96 mg., and lecithin phosphorus between 3.7 and 6.8 mg. per 100 cc. of plasma. During the following week a feeble irregular reticulocyte response was obtained with a maximum of 6 per cent. No appreciable rise of either cholesterol, lecithin phosphorus or red blood cells was observed during or after this abortive remission except that the fluctuations were over a slightly wider range. During a subsequent four weeks' period with the same treatment, the red blood cells varied between 0.9

and 1.6 millions per c.mm., the cholesterol between 89 and 116 mg. and the lecithin phosphorus from 6.2 to 9.6 mg. per 100 cc. of plasma. She was then fed 240 gm. of raw liver pulp. A remission set in promptly with a reticulocyte rise of small magnitude, reaching 8.7 per cent. The slight rise was dependent partially on the fact that a weak response had occurred before and infection complicated the picture. The cholesterol rose promptly to 136 mg., while the lecithin phosphorus fluctuated at the previous low level. A secondary rise of cholesterol to 156 mg. was accompanied by an increase of red blood cells from 1.4 to 2.1 millions per c.mm. without any definite increase in the lecithin phosphorus. The cholesterol level was maintained while the lecithin showed a gradual increase until high normal values were reached. The red blood cells and hemoglobin meanwhile reached normal values. The course taken by this patient's case presents a somewhat confused picture because of complications of bronchitis and cystitis. The remission was delayed but the outstanding feature is that the cholesterol rose promptly when finally the remission set in and the maintenance of the established level.

The second patient with an irregular course entered the hospital with low cholesterol and lecithin values and 1.6 million red blood cells per c.mm. This patient was observed for a period of eight months. The picture was complicated by a pyelitis, cholecystitis, cholelithiasis, and fever during the first month. A remission on a meat preparation was accompanied by a slight increase of the cholesterol level from between 61 and 72 mg. per 100 cc. of plasma to a level between 83 and 104 mg. per 100 cc. during the reticulocyte rise, and an increase of the lecithin phosphorus from a level varying between 5.2 and 6.7 mg. to a level between 5.6 and 8 mg. per 100 cc. of plasma. The remission was not maintained because of obvious inadequate therapy, and a transfusion of blood was given and liver extract administered but not in maximal doses. A second rise of reticulocytes to 15.2 per cent indicated a response but the number of red blood cells remained practically stationary for a period of forty-two days because of infection and insufficient supply of active principle. The average of 18 cholesterol determinations during the period was 81 mg. with a maximum of 125 mg. per 100 cc. of plasma, and a subsequent minimum of 48 mg. per 100 cc. After the infection had subsided, the red blood cells increased slightly with the establishment of a higher level of cholesterol to an average of 104 mg. per 100 cc. Permanent improvement did not occur until optimal doses of potent material were fed. This was accompanied by a further rise of cholesterol to a higher level. The lecithin phosphorus during the second reticulocyte rise increased from an average of 7.1 mg. before to 10 mg. per 100 cc. during the reticulocyte rise, subsequently to decline somewhat, fluctuating between 7.1 and 10 mg. per 100 cc. The fatty acids during this period showed no

definite trend, varying within normal limits during the entire period of observation.

Of the remaining 4 patients with red blood cells between 1 and 2 million per c.mm., entering the hospital in relapse, one obtained a typical although less pronounced rise of cholesterol and lecithin at the time of remission provoked by a test preparation of meat, while another showed a sudden rise of cholesterol late in the remission as indicated by the reticulocyte curve, which rose to 11.6 per cent but tended to be long drawn out. The lecithin rose at the beginning of the remission. A third patient had a remission without specific treatment with a typical increase of cholesterol, while the fourth, observed for three months, also had a spontaneous reticulocyte rise. This latter patient showed low cholesterol value during the entire period. The highest value obtained was 118 mg. per 100 cc. just before the increase of the reticulocytes when the red blood cells were 1 million per c.mm., then declined to a value of 0.073 per cent with 2.9 million erythrocytes per c.mm.

The last case in this group entered the hospital with 1.9 million cells per c.mm. and 170 mg. of cholesterol per 100 cc. of plasma. The red blood cells increased gradually to 4.5 million cells per c.mm., without any change of cholesterol or lecithin phosphorus from the variation of a high normal level. The reticulocytes numbered 7.4 per cent on the day after admission so that one may conclude that a remission had commenced when he entered the hospital.

Group 3. The third group of pernicious anemia cases, 8 in number, had red blood cell counts over 2 million per c.mm. They showed greater variations both in the clinical picture as well as in the course of the lipoids of the blood than the cases comprising Groups 1 and 2. Only 2 of the 8 cases had low cholesterol and lecithin values. One recovered promptly on a kidney diet, with a rise of red blood cells from 3.4 to 4.5 millions per c.mm., without any appreciable rise in reticulocytes, as at this level of red blood cells the reticulocyte response is usually slight, but with a sudden rise of cholesterol from a level below 75 mg. to 146 mg. per 100 cc. of plasma. Nine days later a still higher level was established and this was maintained. The other patient with a low plasma cholesterol at first had a decline of his red blood cells, plasma cholesterol and lecithin phosphorus, then as remission commenced there was a typical rise of cholesterol, while the lecithin phosphorus remained at a comparatively low level for a considerable period, first reaching a normal level when the red blood cells approached 4 millions per c.mm.

Five patients of this group entered the hospital with a moderate anemia and normal levels of cholesterol and lecithin phosphorus in the blood. Dietary procedures that were instituted which can induce remissions were without appreciable influence on the lipoids of the blood. One of these patients reëntered the hospital six

months later with 3.3 million red blood cells per c.mm., and lower values for cholesterol and lecithin phosphorus than on the previous admission. At this time for one month the cholesterol fluctuated back and forth between 104 and 150 mg. per 100 cc. of plasma and the lecithin phosphorus between 7 to 10.4 mg. per 100 cc., although the erythrocytes rose to 4 millions per c.mm., as the result of the feeding of a test preparation of meat partially digested by normal gastric juice. The red blood cells rose from 4 to 4.6 millions per c.mm. when liver extract was administrated and the level of cholesterol became fixed between 143 to 163 mg., and lecithin phosphorus between 8.5 to 12.2 mg. per 100 cc. of plasma during the following four months.

The last case in this group was atypical in that the cholesterol remained at a comparatively low level during the time of observation. The erythrocytes on admission were 2.4 millions per c.mm. The patient was fed daily about 200 gm. of kidney. During a twenty-five-day period the red blood cells rose to 3.4 millions per c.mm., without any increase of the reticulocytes. The cholesterol during this same time varied between 96 and 129 mg. per 100 cc. of plasma with an average of 8 determinations of 115 mg. The lecithin phosphorus averaged 7.8 mg. per 100 cc. of plasma with a minimum of 6.7 and a maximum of 9.7 mg.

Lipoids in Pernicious Anemia Before Definite Relapse. Seven cases diagnosed as early or doubtful pernicious anemia were studied. All of them showed an anemia of slight degree. Three had a plasma cholesterol at the upper limit of normal, 2 had an average normal amount, while 2 showed low cholesterol values. One of the latter with a red blood cell count of 4.1 millions per c.mm. had cholesterol values between 76 to 103 mg., and lecithin phosphorus between 9.1 to 10.4 mg. per 100 cc. of plasma, while the other had a range of red blood cells over a month's period (13 determinations) of 3.6 to 4.7 million red blood cells per c.mm. The cholesterol varied between 98 and 126 mg., and the lecithin phosphorus from 8.3 to 11.1 mg. per 100 cc. of plasma. Thus, in these 2 cases, which were not treated with liver or a potent substitute, the cholesterol was low, and remained so without any tendency to increase, while lecithin varied within normal limits.

Lipoids in Normal Adults Fed Liver and Liver Extract. Two healthy male individuals were studied in addition to the cases of pernicious anemia. Daily cholesterol, lecithin phosphorus and fatty acid determinations were made. For the blood counts I am indebted to Drs. W. C. Townsend and G. R. Robb. The lipoid determinations were made on the same specimen of venous blood used for the blood counts. In addition three daily red blood cell counts were made on the capillary blood. The counts obtained from both the venous and the capillary blood showed practically identical values. The reticulocytes remained at a normal level.

The daily variation in red blood cells, cholesterol, lecithin phosphorus and fatty acids is illustrated in Chart III.

From an examination of the graphs which are entirely comparable for both individuals, it is evident that neither optimal amounts of liver nor liver extract for pernicious anemia patients cause in the normal person a change in the level of the red blood cells or the lipoids. The average of the cholesterol in one case was 132 mg. per 100 cc. of plasma with a minimum of 121 mg. and a maximum of 156 mg., while the average of the other was 155 mg. per 100 cc. of plasma with a minimum of 139 and a maximum of 175 mg.

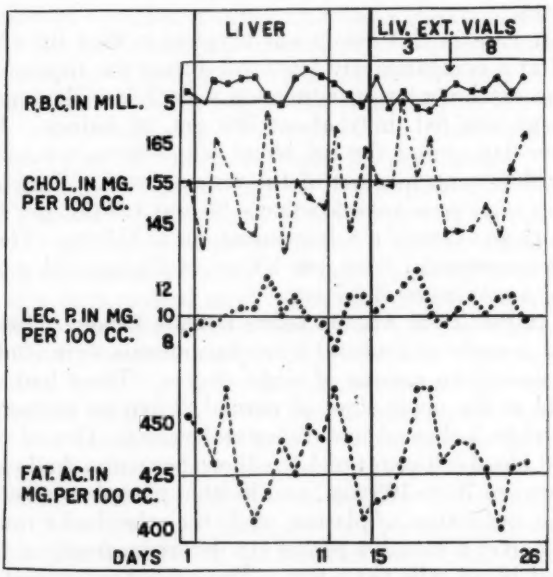

CHART III.—The variation of red blood cells, cholesterol, lecithin phosphorus and fatty acids in a healthy adult male, with liver and liver extract added to the diet.

The amount of liver fed was gradually increased from 200 to 300 gm. Each vial of liver extract represents 100 gm. of Liver Extract 343, N.N.R. Neither liver nor liver extract was administered on the first day or between the eleventh and fifteenth days.

Discussion. The findings in this series of cases of pernicious anemia show that the cholesterol in the blood plasma is low in relapse but that a sudden rise to a higher level, which later increases and is maintained, occurs at the onset of the remission. The increase of the cholesterol, as a rule, is concomitant with the reticulocyte response and apparently proportional to the intensity of this reaction. The increase of the cholesterol is not dependent upon whether the active principle effective in pernicious anemia is fed in one form or another, nor upon the number of red blood cells in the peripheral blood, but upon the change that takes place in the organism at the onset of a remission. It is, however, proportional to the amount fed

of the active principle effective in pernicious anemia. Suboptimal doses call forth an irregular response of the cholesterol, while optimal doses increase and maintain the cholesterol at a normal or high level. As in the case of the reticulocytes, the response of the cholesterol is of greater magnitude the lower the red blood cell count. After the remission has commenced, a change from liver extract to liver, kidney or meat, partially digested with gastric juice, which contain a considerable amount of cholesterol does not influence the level of cholesterol except when the remission has been weak because of inadequate dosage and the cholesterol level has been fluctuating within wide limits. In such cases, the administration of adequate doses of the effective principle caused the level to become steady at normal figures.

An incomplete response of the reticulocytes without actual improvement in the patient calls forth a slight increase in the cholesterol temporarily with a subsequent fall to the previous level. Infection, delaying or giving an irregular response to treatment, like inadequate dosage, is reflected in an irregular cholesterol and lecithin phosphorus curve with wide fluctuations.

In healthy individuals, the administration of large doses of liver and liver extract does not cause an appreciable change of the level of cholesterol. From the examination of Chart III it is evident that moderate daily fluctuation occurs in the cholesterol level. Thus by establishing the relation of the cholesterol to the onset of remission in pernicious anemia a probable explanation, at least, in this disease, has been obtained for the apparent lack of correlation of the cholesterol to the severity of the anemia. Normal or high values for plasma cholesterol with low red blood cell counts in pernicious anemia indicate that remission is taking place.

Recent reports from Germany confirm the above observations. Adler and Schiff[19] found that the cholesterol in the blood of pernicious anemia patients increased in quite the same way when liver extract or raw liver was fed. Contrary to the observations recorded here, they found an increase of plasma cholesterol in healthy persons partaking of a liver diet. In animals, Adler and Schiff noted that "hepatrat," a liver concentrate, as well as whole liver, increased the blood cholesterol but the bile cholesterol did not vary after the administration of either the extract or whole liver. Consequently these authors concluded that the increase of cholesterol in the blood after administration of liver and liver extract was not due to an alimentary hypercholesteremia but depended upon the intermediary metabolism. The same conclusion was drawn by Wesselow.[40] Beck[41] found that in patients whose erythrocyte count was not influenced, the cholesterol content of the blood did not change. That a high fat meal does not increase the cholesterol in the blood in pernicious anemia has been shown by Broun[49] who examined 4 patients at frequent intervals during eight hours after a high fat meal.

Very few facts are available to adequately explain the low values of cholesterol in pernicious anemia and the sudden change at the onset of remission. The blood volume in pernicious anemia is usually reduced[50] while the plasma volume remains essentially normal. Wesselow[40] observed that the absolute plasma volume showed a considerable degree of constancy during the progress of treatment with liver, with a slight tendency to fall during the later stages of improvement.

In most cases of pernicious anemia, digestive disturbances are present. Nevertheless, Kahn and Barsky[51] and Gibson and Howard[25] found a normal fat content of the stools. Cornell[52] came to the conclusion that there is no evidence of abnormal metabolism of simple fats and a satisfactory usage of fat although there is a tendency to overstorage and pathologic infiltration by fat in active tissues. The relation of frequent and loose stools to the cholesterol content of the blood has been investigated by Schnabel.[36] In 3 cases given no other diagnosis than diarrhea he found high normal values, while patients with achylia gastrica had cholesterol within normal limits.

However, in pernicious anemia Reicher[53] found an increase of cholesterol in the stools. In a patient with pernicious anemia in a four-day control period a daily average of 0.6333 gm. of cholesterol was excreted, while after a daily addition of 3 gm. of cholesterol to the diet in an eight-day period, only an average of 0.5484 gm. was excreted, indicating a retention. In this connection, it is of interest to note that Reicher reported improvement in pernicious anemia after administration of cholesterol. In a control patient with mitral insufficiency, the daily average during a control period was 0.2908 gm., while the addition of 3 gm. of cholesterol increased the average daily output over a four-day period to 2.0766 gm.

In cholesterol-balance experiments on 3 pernicious anemia patients, Beumer[54] found a negative balance in each case of 0.025, 0.119, and 0.207 gm. respectively. A healthy person showed a negative cholesterol balance over a ten-day period of 0.081 gm. Normally a negative balance of cholesterol is present in man, but no conclusion can be drawn from the above results in pernicious anemia as no data are given to indicate the condition of the patients, except that they were "at a standstill showing no progress." This is realized by Beumer, who states that the remission, crisis or a stationary condition may influence cholesterol metabolism. On the other hand, in nephrosis, Beumer[54] demonstrated a retention. This is of interest as in nephrosis the cholesterol in the blood is increased.

Loss of cholesterol in the stools has been reported by Rosenbloom and McKelvy[55] in a patient with hemolytic icterus. A diet containing 5.22 gm. of cholesterol, determined by the method of Windaus, was given. The cholesterol obtained in the feces was 12.27 gm., giving a negative balance of 7.05 gm.

Barat[56] demonstrated in 5 cases of pernicious anemia that the cholesterol in the bile was greatly increased. Rosenthal[57] explains the decrease of cholesterol in the blood in hemolytic jaundice and pernicious anemia as probably due to the loss of cholesterol through the bile. As a rule, blood cholesterol in hemolytic jaundice is low.

Very few data are available on the blood lecithin of pernicious anemia. Beumer and Bürger,[58] in 1913, found low values. Bloor and MacPherson[39] in 7 pernicious anemia patients found values for lecithin at the lower normal limit or below normal. In the plasma of 3 cases in which the number of corpuscles was low, there were constantly low values for lecithin, while in a fatal case the lecithin increased in the plasma as the number of corpuscles diminished. The same was observed in one case in this series. Feigl[59] reported a study of 17 cases of pernicious anemia patients with determinations of the fatty acids, lecithin and cholesterol in the blood plasma. Twenty-four determinations are recorded. Low lecithin values were found in 7 patients and above normal in one. The rest were within normal limits. In the patient, with high lecithin values, the cholesterol and fatty acids were also high with a red blood cell count of 400,000 per c.mm., and 10 per cent hemoglobin. In all the cases with low lecithin values the cholesterol was correspondingly decreased, although a normal amount of lecithin was present with subnormal cholesterol in one case. The fatty acids were increased in 10 patients, below normal in 2, and normal in 5. No correlation could be established between the level of the erythrocytes and hemoglobin on the one hand and the lipoids on the other. The 3 patients with the lowest red blood cell counts showed fatty acids below normal, normal and above normal. Bloor and MacPherson[39] could not verify the abnormally high figures for fat in the blood of pernicious anemia patients reported by King.[60] They found the fatty acids to be within normal limits while total fat was increased. Marked abnormalities were found mainly in the plasma, the corpuscles in anemia as in most other conditions tending to preserve a constant lipoid composition. The relationship of fatty acids, lecithin and cholesterol to each other in the plasma and corpuscles has been reviewed by Bloor.[20] In lipemia[61] the increase of cholesterol and lecithin follows rather closely the increase of fat, but the values of cholesterol and lecithin remain high after the fat has decreased to normal and falls to normal only after several days. This slower rate of removal of lecithin and cholesterol as compared with fats points to a different mechanism for the removal of the two groups of lipoids.

In the present study the lecithin phosphorus followed the cholesterol closely in many instances, being low in the relapse of pernicious anemia and increasing suddenly at the onset of remission. In other cases the lecithin was within normal limits when low cholesterol values were found. In all cases no significant change was

observed in the fatty acids, the same fluctuations being observed both before and during and while in remission. The sudden rise in the lecithin, before any appreciable increase of red blood cells makes one question in how far the number of red blood cells in the peripheral blood regulates the level of the lecithin phosphorus in the plasma.

A few suggestive reports on the relation of the lipoids to cell proliferation ought to be cited. Cholesterol [62, 63] has been claimed as an agent that can increase the growth of cells while lecithin retards growth of carcinoma cells.[63] On the other hand, Masing[64] suggested the use of the phosphorus content of the erythrocytes as a criterion of the presence of newly formed red blood cells. A higher percentage would indicate a stimulation of the erythropoietic organs. Young red blood cells as well as immature white blood cells contain more phosphorus than mature cells.[65, 66] Bloor[67] found an increase of lipoid phosphorus in the young red blood cells of rabbits after bleeding, but whether this increase was characteristic of young erythrocytes or due to the lipemia he was not prepared to say.

An interesting experiment has been reported by Sundstroem and Bloor.[68] In animals subjected to low barometric pressure experimentally the lipoid phosphorus decreased on an average 13.2 per cent when compared with the constancy of the lipoid phosphorus in controls (average 1.6 per cent). These figures led the authors to conclude that the decrease of the lipoid phosphorus is due to the low oxygen tension, as digestion and work were excluded. The enrichment of the circulating red blood cells with lipoids, that would result in impoverishment of these substances in the plasma did not occur, as it was found that the greatest decrease in plasma lipoids was accompanied by a proportional decrease of corpuscle lipoids. Sundstroem and Bloor thought that the phospholipoid was deposited in the hematopoietic organs, as elimination through the kidney was excluded, and the plasma volume was concentrated rather than diluted. It has been shown that lecithin plays some rôle in erythropoiesis since the bone marrow contains comparatively large amounts and it is higher in the red marrow of the young than the aged.[69] The enrichment of the erythropoietic organs with lipoid material, Sundstroem and Blood suggested might be the first phase of a stimulation of these organs resulting from a lowering of the atmospheric pressure.

Some evidence that also cholesterol is retained and perhaps deposited in a hyperplastic bone marrow has been given by Rewald.[70] He examined the femoral bone marrow for cholesterol in one case of pernicious anemia. He found the water content enormously increased and the dry substance correspondingly decreased, but in spite of this the cholesterol in the dried substance was not decreased constituting 0.9288 per cent as against 0.6550 per cent in a patient

who died from lysol poisoning. The possibility of the utilization of the lipoids in the formation of the enormous number of megaloblasts in the bone marrow in pernicious anemia must be thought of. The extent of this new formation is realized when it is considered that the bone marrow, the full potential capacity of which is realized in pernicious anemia, is inferior in weight only to the skeleton, muscles and blood.[71] For each gram of blood there is 0.55 gm. of bone marrow.

The cholesterol and other lipoid content of various organs in pernicious anemia has been reported increased by some[72, 73] while others have found decreased values.[74, 75] Piney[76] states that in pernicious anemia the liberation of lipoids from the destruction of red blood cells is probably the direct cause of the intense fatty changes found in the liver, heart and other organs. He considers that the normal mechanism for storage of fat is stimulated.

In a review[43] of the relation of the reticuloendothelial system to cholesterol metabolism, it was found that hypocholesteremia can be produced by the stimulation of this system with colloidal substances. Cornell[52] reflecting on the various data brought out by recent work suggests the possibility that in pernicious anemia the total hematological manifestation may result from abnormal cell metabolism on the part of the reticuloendothelial system. There is suggestive evidence that cholesterol excretion and perhaps also the deposit in the tissues are increased, and that both cholesterol and lecithin may participate in the formation of new red blood cells. Whether there is a decrease of the elimination of cholesterol through the bile and the feces at the onset of remission is unknown. There exist no data concerning the excretion and balance of cholesterol at this stage of the disease.

The elucidation of what actually occurs in the patient with pernicious anemia at the onset of remission and during its progress will bring forth valuable information not only as to the disease pernicious anemia but also as to the regulatory mechanism of cholesterol and lecithin within the body.

Conclusions. 1. Cholesterol, lecithin phosphorus and fatty acids of the blood have been determined at frequent intervals in 26 cases of pernicious anemia, especially with reference to the remission. Eight early or doubtful cases of pernicious anemia and 2 normal adults have been studied in like manner.

2. In pernicious anemia in relapse the cholesterol and lecithin phosphorus are low, while the fatty acids show variations apparently within normal limits.

3. In typical cases of pernicious anemia in marked relapse the cholesterol rises suddenly at the onset of the remission. The rise is concomitant with the response of the reticulocytes and as a rule is proportional to the intensity of the remission and of greater magnitude the lower the red blood cell count.

4. The increase of cholesterol occurs before there is a definite increase in the concentration of erythrocytes and hemoglobin. It is independent of transfusion of blood and is called forth by an adequate dose of potent material effective for pernicious anemia. The results are the same no matter whether the potent material is fed in the form of liver, kidney, liver extracts, or certain preparations of meat partially digested with normal gastric juice. Thus the increase is associated with the induction of remission.

5. In cases fed suboptimal amounts of potent material effective in pernicious anemia the cholesterol level showed wide fluctuations, but when addition of optimal amounts was made there occurred a prompt decrease in the fluctuations and such dosage then maintained the cholesterol at a normal level. In abortive remissions there is a slight rise of cholesterol at the time of the incomplete response of the reticulocytes with a return to the previous low level. To obtain a normal level of cholesterol a satisfactory type of remission is necessary.

6. After the rise of cholesterol, the increase red blood cells is not followed by a proportional increase of cholesterol although in individual cases values above normal may be obtained.

7. Infection, when delaying or causing an irregular remission, is reflected in an irregular response of the lipoids of the blood.

8. The lecithin phosphorus as a rule follows the cholesterol, although exceptions occur. Occasionally normal values of lecithin are found with subnormal values of cholesterol or the lecithin phosphorus may rise somewhat more slowly.

9. The fatty acids do not show any significant variation during remission, the same fluctuations around a normal level being obtained before and after the onset of remission.

10. In early or doubtful cases of pernicious anemia with a slight anemia, the level of cholesterol may be high or normal and occasionally somewhat lower than normal.

11. In two healthy men, studied over a considerable period, the addition of liver or liver extract to the diet did not influence the level of cholesterol, lecithin phosphorus, fatty acids or number of erythrocytes and reticulocytes.

12. It appears that the low cholesterol and lecithin phosphorus content of the plasma in complete relapse of pernicious anemia is dependent on the disease process and that the establishment of a normal level of the lipoids is closely associated with the onset of remission or the change that occurs when the reticulocytes respond to therapy and when there is a decrease of bilirubin in the plasma and sudden improvement of the patient. The elucidation of the cause of these changes will throw light on the regulatory mechanism of lecithin and especially cholesterol.

13. The total inconsistency of the reports in the literature concerning the relation between the blood cholesterol in pernicious

anemia, and the concentration of the erythrocytes and hemoglobin, is explained by the results recorded. Normal or even high values may be present with severe anemia, provided remission has begun.

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PAROXYSMAL VENTRICULAR TACHYCARDIA.

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Paroxysmal ventricular tachycardia has been described now for twenty years. Although case reports have been more frequent recently, only 65 undoubted cases could be found in the literature to this time. It is the purpose of this paper to summarize some of

the data of these cases and to add 2 cases, 1 studied with regard to the control of the rapid rate, the other exhibiting bidirectional electrocardiograms.

Definition. Paroxysmal ventricular tachycardia can be recognized definitely only by means of the electrocardiograph, although certain clinical signs make the diagnosis probable. With the electrocardiograph, several criteria, originally outlined by Robinson and Herrmann,[1] are necessary for the diagnosis. There must be evidence that the impulses producing the tachycardia arise within the ventricles, in which case the form of the *Q–R–S* complexes will be distinctly abnormal. This abnormal form, however, cannot be taken as pathognomonic, as it occurs in cases of bundle-branch block and in cases of simple auricular tachycardia (White and Stevens,[2] Lewis,[3] Marvin and White[4]). The identification of independent auricular waves, occurring at a slower rate than the ventricular waves, is in favor of a ventricular origin of the tachycardia. If in the interval between paroxysms the ventricular complexes are normal and there are isolated premature ventricular complexes of the same shape as those of the paroxysm, the diagnosis can be made certain. Additional evidence may be obtained by observing that the onset and offset of the tachycardia bear the same relation to the slow rate as do isolated premature systoles, and that there is a slight irregularity in the rapid rate, noted by Strong and Levine,[5] which is not to be found in other forms of paroxysmal tachycardia.

Experimental Ventricular Tachycardia. Lewis has produced paroxysms of tachycardia of ventricular origin in both dogs and cats by the ligation of a coronary artery, particularly the right coronary,[6] and with Levy has shown that the same effect may be produced by the combination of intravenous adrenalin and the inhalation of varying tensions of chloroform vapor.[7] Rothberger and Winterberg have found that after sensitization of ventricular foci of impulse formation with barium chlorid, either direct stimulation of the accelerator nerves or adrenalin will produce a ventricular tachycardia.[8] Gold was unable to produce this irregularity by the use of digitalis following ligation of a coronary artery in cats.[9]

Clinical Ventricular Tachycardia. Since Lewis' first 2 cases,[10] 63 additional cases have been described in the literature.[1,4,5,11–38] Half that number of cases have also been recorded in which entirely adequate diagnostic criteria were not present, although many are probably true cases of the arrhythmia.[5,10,13,14,17,18,24,39–49] Clinical history was available in 64 undoubted cases, including the 2 cases presented below.

Age Incidence. This is shown graphically in Fig. 1. Sixty per cent of the cases occurred during the fifth and sixth decades, 14 per cent before this period and 26 per cent later in life.

Sex Incidence. Forty-three, or slightly over two-thirds of all the cases occurred in members of the male sex.

Morphologic Pathology. In 11 of the 64 cases there was no clinical or laboratory evidence of pathology other than the arrhythmia. The remaining 53 cases all presented evidence of cardiac pathology:

Type of heart disease.	Number of cases.
Cardiovascular-hypertensive disease	16
Coronary disease	12
Rheumatic heart disease	8
Arteriosclerotic heart disease	4
Syphilitic heart disease	4
Thyreotoxic heart disease	2
Type of heart disease not clear	7

Functional Pathology. Heart failure, either of the congestive or anginal type, was present when the tachycardia was first noted in 45 instances. Auricular fibrillation was present in 21 cases and auricular flutter in 2.

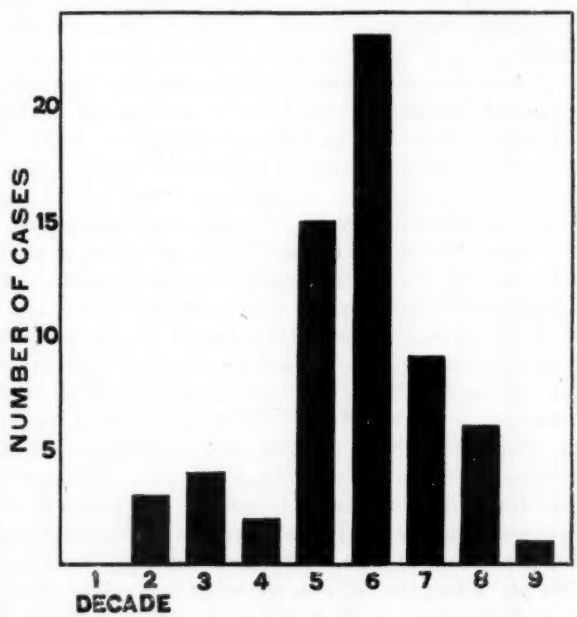

FIG. 1.—Age incidence by decades of paroxysmal ventricular tachycardia.

Digitalis had been administered before the onset of the tachycardia to 50 per cent of the cases, all in the group presenting definite cardiac disease. In some cases the dosage was excessive, while in others it was entirely too small to produce any effect. In a number of cases the withdrawal of digitalis was followed by a cessation of the tachycardia, while its subsequent use resulted in a return of the rapid rate, indicating that in the presence of organic heart damage

this arrhythmia may be one of the toxic manifestations of digitalis administration.

When the electrocardiograms are of the usual type (Fig. 3) most writers have considered that a single irritable ectopic ventricular focus has been the mechanism responsible for the tachycardia. In 18 of the 64 cases bidirectional alternation of the complexes occurred[16,18,22,24,26,29,33,34,36,37] similar to that in the second lead of Fig. 2. Alternate blocking of the left and right branches of the conduction system, at first suggested as the mechanism of this condition, with a single focus of stimulus production, seems unlikely. Multiple foci of impulse formation or circus movements in the ventricle similar to those in the auricle in auricular fibrillation and flutter have been given most emphasis in the recent excellent discussions of Palmer and White[33] and Marvin.[37]

Clinical Diagnosis. Suspicion of the presence of paroxysmal ventricular tachycardia must be aroused whenever a rapid, almost or completely regular, rate supervenes in a case of long-standing heart disease, particularly if large doses of digitalis have been used, or in a case of coronary occlusion. Levine and his co-workers[5,38,50] have emphasized certain aids to bedside recognition. There is a slight irregularity, frequently noted in auscultation, which is found in tachycardia of ventricular origin, not to be found in other forms. At the same time the quality of the first heart sound may perceptibly vary in different cycles. Vagal stimulation and ocular pressure are never effective in terminating a paroxysm of ventricular tachycardia, thereby offering a third differential measure. Positive diagnosis can only be made by the electrocardiograph.

Treatment. Only one therapeutic measure has been successfully employed in terminating ventricular tachycardia—quinidin, usually used as the sulphate. Paroxysms were controlled in all 16 cases in which it was employed.[15,17,20,21,23,25,27,28,29,30,32,35,38] Doses as high as 7.5 gm. a day have been utilized, while maintenance has been sometimes possible on as low as 0.2 gm. per day. Dosage must be adjusted to the individual case, repeating the administration in increasing amounts every few hours, until the paroxysm is controlled or alarming symptoms appear. Although this may seem dangerous therapy, no bad effects have been recorded due to the drug in this condition, and in many cases in which the rapid rate was quickly producing myocardial exhaustion, the use of it has been life-saving. It is interesting to note that in the older literature on quinidin in the treatment of auricular fibrillation, the possibility of ventricular tachycardia or fibrillation was mentioned. One such case exists in our records, in which the withdrawal of quinidin resulted in a termination of the tachycardia. This paradoxical action has not been adequately explained.

Prognosis. Of the 11 cases showing no pathology other than the arrhythmia, all were living at the time of publication of the reports,

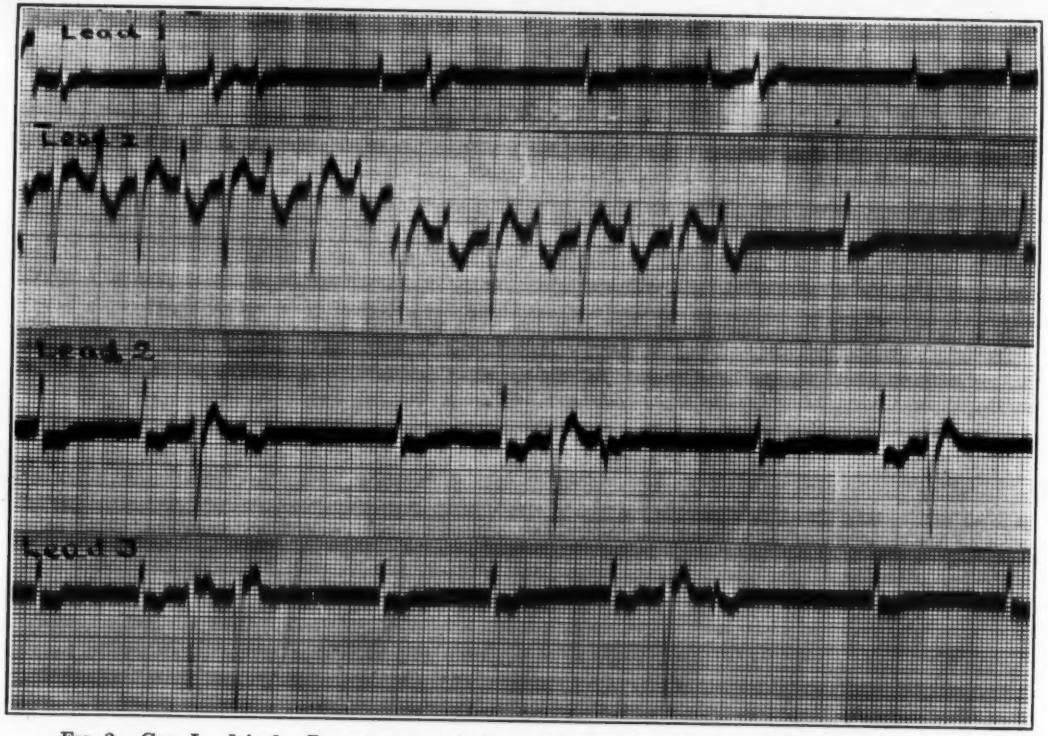

FIG. 2.—Case I. July 2. Premature ventricular systoles, Leads 1, 2 and 3. Paroxysm of ventricular tachycardia showing bidirectional alternation, Lead 2.

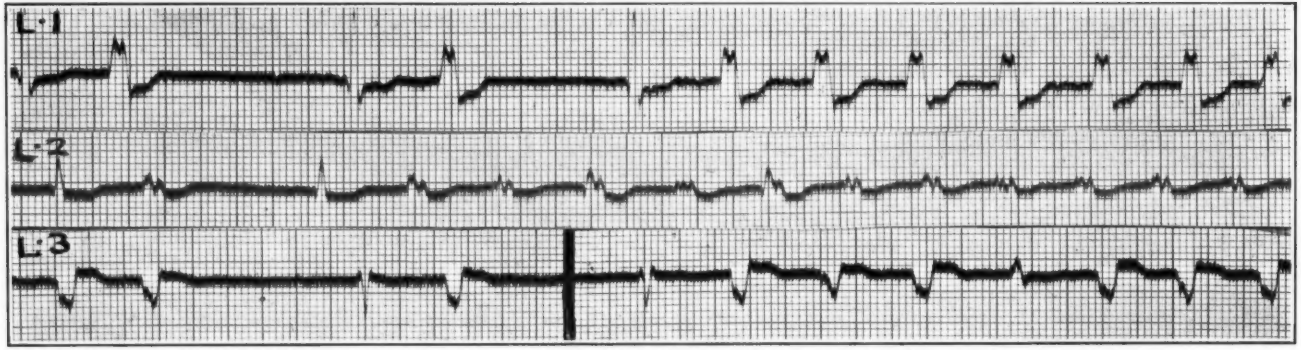

FIG. 3.—Case II. September 25. Paroxysms of ventricular tachycardia and bigeminy, Leads 1, 2 and 3.

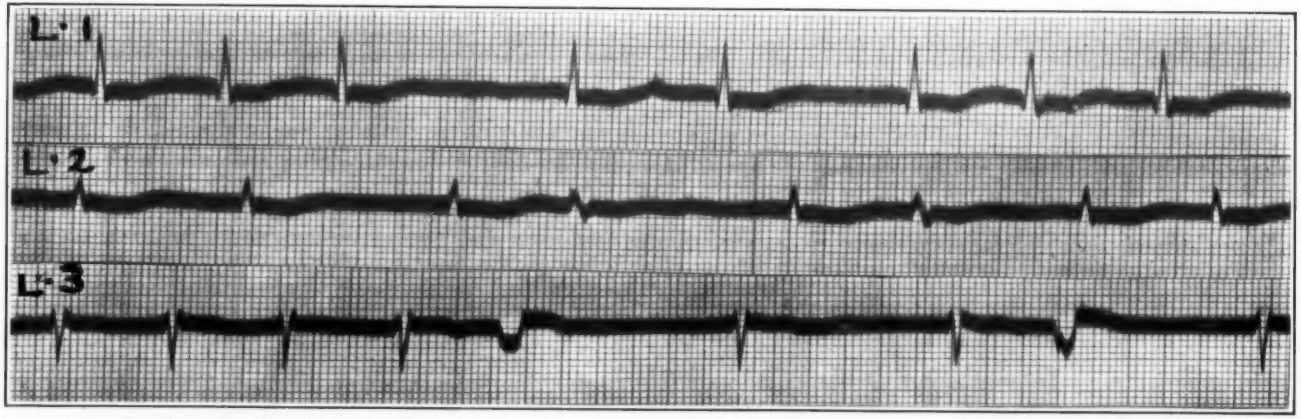

FIG. 4.—Case II. October 8. Quinidin, 1.2 gm. daily. Auricular fibrillation with occasional ventricular premature systoles.

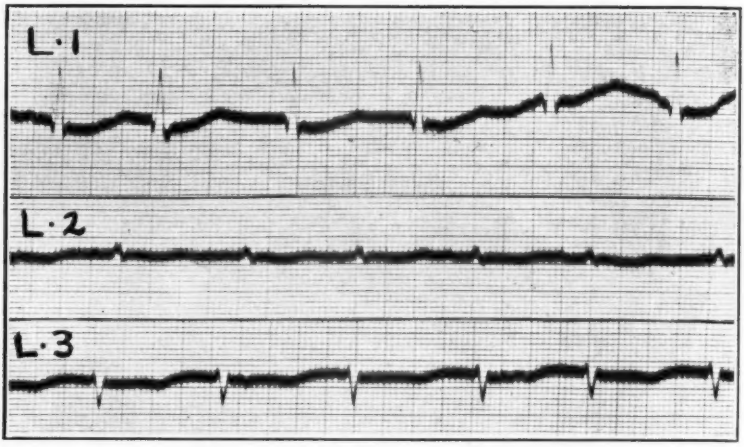

FIG. 5.—Case II. October 10. Quinidin, 1.6 gm. daily. Very slow fibrillation. No premature systoles.

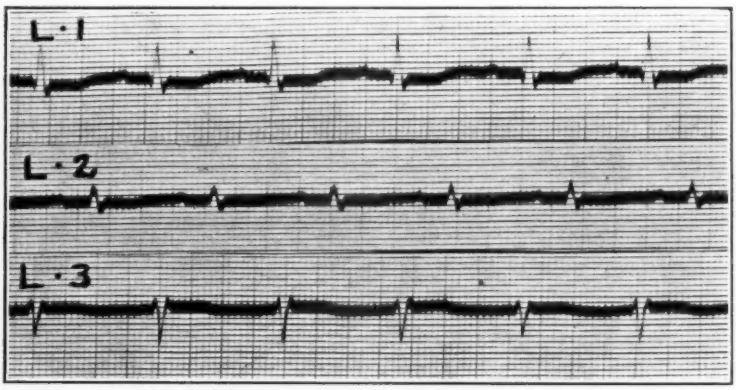

FIG. 6.—Case II. October 15. Quinidin, 2 gm. daily. Normal sinus rhythm.

indicating that in the absence of gross cardiac disease this type of paroxysmal tachycardia does not give a bad outlook.

Of 50 cases with organic heart damage, 40 or four-fifths, were dead within three hours to six months of the onset of the tachycardia, with an average of twenty-four days. Most of these received no specific treatment. Of the 16 cases receiving quinidin only 3 died.

Report of Cases. CASE I.—W. O., a teamster, aged forty-nine years, was admitted June 12 with a complaint of shortness of breath. The past history was negative; venereal infection was denied. A wife and two children were alive and in good health. Nine weeks prior to his admission he had experienced gripping sensations in his chest accompanied by a feeling of suffocation and shortness of breath. From the onset he had about one attack a day, sometimes associated with localized precordial pain, often brought on by exertion. He went to the outpatient department of another institution where he was given intravenous and intramuscular injections following a blood test. Seven weeks from the onset orthopnea appeared, gradually becoming quite severe.

On admission, he was somewhat dyspneic upright in bed. The right pupil was larger than the left and reacted sluggishly to light. The carotids pulsated markedly as did the left subclavian. There was no tracheal tug. The heart was markedly enlarged, 12 cm. to the left in the sixth interspace, with the retromanubrial dullness measuring 8.5 cm. The sounds were of poor quality, regular, rate 100. Systolic and diastolic murmurs could be heard at the apex and a to-and-fro murmur at the base, loudest to the right of the sternum. The radial pulses were regular, synchronous and equal. The blood pressure was 145 systolic and 55 diastolic. The liver edge was palpable 10 cm. below the costal margin. There was no fluid in the abdomen, and slight pitting edema of both legs. The urine was negative and the blood Wassermann positive. The diagnosis of syphilitic heart disease, aortitis and dilatation of the aorta was supported by roentgenologic study.

Tincture of digitalis was given by mouth, 16 cc. the first day and 4 cc. daily thereafter for one week. The patient seemed to be fairly comfortable in bed, with occasional attacks in which there was a sense of suffocation. However, ten days after the discontinuance of digitalis, a suggestive fluid wave appeared in the abdomen, and digitalis was recommenced, 24 cc. of the tincture being administered during the next forty-eight hours. Following this, the pulse developed a rapid slight irregularity characteristic neither of auricular fibrillation or flutter. Electrocardiograms taken at once showed the rare form of ventricular tachycardia with bidirectional alternation of the complexes seen in Fig. 2, and periods during which slow supraventricular beats were interrupted by numerous premature systoles of ventricular origin. Digitalis was omitted and no other medication employed. Two days later the pulse was slow and the patient was free of symptoms referable to the rapid rate. Four days after this sudden death occurred.

Autopsy revealed an adherent pericardium, a normal myocardium and endocardium, and normal coronary arteries. There was typical syphilitic puckering, commencing in the midportion of the ascending arch of the aorta and two thin-walled saccular dilatations, each about 1.5 cm. in diameter were present. The liver and spleen showed passive congestion. Other organs were not remarkable.

CASE II.—G. R., a retired laborer, aged seventy-three years, was admitted September 16, complaining of shortness of breath and precordial pain. The past history was negative for rheumatic and venereal infection. Three

children had died in infancy; the fourth was adult, living in good health. During the ten months preceding admission, he had suffered from shortness of breath upon exertion and edema of the legs; this had become markedly exaggerated in the last two months and orthopnea had appeared. On the morning of admission he had had a very severe attack of sharp, distinctly localized precordial pain.

Examination showed a very seriously ill man, quite orthopneic, cyanosed, with distended, irregularly pulsating veins in the neck, fluid in both pleural cavities, ascites, a liver 4 cm. below the costal margin, and massive edema from the abdominal wall down. The pupils were very slightly irregular and reacted sluggishly to light. The heart was markedly enlarged, the retromanubrial dullness being 8 cm. and the apex in the fifth interspace about 12 cm. to the left of the midsternal line. At the apex a dull systolic murmur replaced the first sound and the second seemed distant. At the base the sounds were slightly clearer, with an accentuation of the second sound to the right of the sternum. The peripheral vessel walls were thickened and the fundal arteries very slightly tortuous. The pulse was totally irregular, with many feeble beats, and a deficit of 20 at the wrist. The apex rate was always above 120. The brachial blood pressure was 160 mm. systolic for the average strong beats which were noted, although many were lower. The blood Wassermann was negative. The urine showed a faint trace of albumin and no formed sediment. A teleoroentgenogram confirmed the size of the heart. The diagnosis was arteriosclerotic heart disease, auricular fibrillation, marked decompensation and questionable coronary occlusion.

Digitalis, 1.1 gm., was given on admission and 1.6 gm. during the following four days. Marked improvement occurred in the general condition of the patient, the pulse deficit disappeared and the rate fell to 80. Purine diuretics were employed with moderate diuresis, but considerable edema persisted. A daily dose of 0.1 gm. of digitalis was instituted. On the fifth day of this dosage, Cheyne-Stokes respiration made its first appearance and the pulse rate showed an alternation between a rapid, perfectly regular rate of 140 and a slow, irregular bigeminy. Electrocardiograms taken at this time showed periods of ventricular tachycardia alternating with a slow, irregular coupling, consisting of a supraventricular beat followed by a premature ventricular systole, this phase exactly as in digitalis intoxication (Fig. 3). Digitalis was discontinued.

Clinically, there seemed to be a vague correlation between the Cheyne-Stokes respiration and the rate changes. Simultaneous pneumographic and electrocardiographic tracings indicated no definite relationship between cardiac and respiratory phases except that in general there were as many alternations between tachycardia and coupling as there were between apnea and dyspnea.

Carbon dioxid inhalation was given to the patient later in the day with the production of deep, perfectly regular hyperpnea, but without any effect on the alternation of paroxysms of tachycardia. Adrenalin (1 cc.) given subcutaneously produced no effect upon either the respiration or the pulse. Vagal and ocular pressure likewise proved ineffectual. Since Gold and Otto had reported the almost complete disappearance of digitalis bigeminy under atropin[51] and Reznik and Lathrop had reported a case in which Cheyne-Stokes respiration produced an effect on the cardiac rhythm through the vagus[52] atropin was administered subcutaneously in dosage of 2.2 mg. No effect on either heart or respiration was produced in forty minutes when the dose was repeated and observations continued. Although well-marked signs of atropin effect were noted in dryness of the mouth and dilatation of the pupils, the electrocardiograms continued to show the same rhythmic changes.

After the paroxysms of ventricular tachycardia had persisted for ten days in spite of withdrawal of digitalis, the general condition of the patient was decidedly worse. Marked venous stasis was evident and edema was even greater than on admission. Quinidin therapy was decided upon and the sulphate administered by mouth. Under dosage of 0.8 gm. per day slow bigeminal rhythm became the dominant mechanism, with rare paroxysms of tachycardia. With a dose of 1.2 gm. daily the rhythm changed to that of slow fibrillation with some premature ventricular systoles (Fig. 4). Increasing the quinidin to 1.6 gm. per day produced the electrocardiogram shown in Fig. 5, suggestive of a very slow auricular fibrillation, and finally with a daily dose of 2 gm. normal sinus rhythm was restored (Fig. 6). In spite of the slower regular rate and the absence of excessive venous stasis the patient failed to show any improvement and sank slowly into a stupor followed by exitus. Permission for autopsy could not be obtained. In this case the relationship of the paroxysms of tachycardia to the digitalis medication seems much more obscure than in the preceding case. Whether the earlier administration of quinidin might not have been of greater value cannot be said, but the ten days of tachycardia had undoubtedly weakened what little cardiac reserve had been present at the onset.

Summary. 1. Sixty-three cases of paroxysmal ventricular tachycardia found in the literature and 2 of the writer's here presented have been analyzed.

2. No common single etiologic factor could be discovered, but 84 per cent of the cases occurred in patients suffering from organic heart disease, and of these 60 per cent had been treated with digitalis prior to the onset of the tachycardia.

3. In the absence of organic heart disease the prognosis of paroxysmal ventricular tachycardia is good.

4. Probable diagnosis may be made at the bedside in seriously ill patients, and quinidin therapy instituted, with uniform success in ending the tachycardia.

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THE USE OF BACTERIOPHAGE FILTRATES IN THE TREATMENT OF SUPPURATIVE CONDITIONS.

(Report of 300 Cases.)

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An experience involving approximately 300 cases treated by the local application of bacteriophage filtrates to a wide variety of suppurative lesions permits one to make a number of observations concerning the type of case suitable for such treatment, the best method of application, and the therapeutic results attained, which a smaller series would hardly justify. Many other cases in the care of colleagues have been reported to me but not made the subject of

this report except in a few instances, when they were well-worked out. In the main, our results have been surprisingly good.

Most of the first 50 cases treated received active strains of bacteriophage as determined by tests *in vitro* against the autogenous cultures. In more recent work, we have wished to get the treatment out of the laboratory stage, and have for the most part used polyvalent stock preparations made by mixing various filtrates representing several bacterial cultures (Staphylococcus and Bacillus coli), and as many homologous bacteriophage strains. The advantage of the stock preparation is obvious in that it is immediately available when needed, is much less expensive, and can be made in large amounts and kept rather indefinitely. Stock preparations have seemed to be just as good as those prepared for a specific case, except that they have not "hit" quite so certainly. When the stock preparation has proved ineffective, we have tested it out against an autogenous culture of the offending organism to determine whether or not it would cause lysis. In nearly every such case we have found that the stock preparation was not active or was very slightly so. If then an active bacteriophage strain from some other source could be found it was used, and if it was effective was then added to the stock preparation for future use. The sources of our bacteriophage strains have been a laboratory strain of great potency (the original Gratia strain) and other strains isolated by ourselves from the pus of spontaneously healing lesions, or from the sewage of the city of Indianapolis.

We shall not attempt to discuss in this paper the problem as to how the filtrate acts in achieving the results obtained, but wish to say that we appreciate the fact that there are other factors than the pure Twort-d'Herelle phenomenon which may be involved. The filtrate which we have used has been a meat extract or meat infusion peptone broth, pH 7.6 to 7.8 when made, in which bacteria have grown for from two to twenty-four hours before being partly or completely lysed by the addition of active bacteriophage, and which has then, after twenty-four hours, been passed through a Seitz or a Berkefeld filter to sterilize and remove material in suspension.

The results which we have seen may have been due to one or more of the following theoretical possibilities:

1. The action of the bacteriophage as a lytic agent capable of destroying the offending organisms in the manner described originally by d'Herelle.[1]
2. An antivirus effect such as Besredka[2] has described.
3. The effect of an extremely available antigen in the form of the dissolved bacterial bodies as suggested by Arnold and Weiss.[3]
4. The induction of the offending organism into an avirulent phase as a result of the microbic dissociation enforced by the presence of the bacteriophage as pointed out by Hadley.[4]

5. The effect of the stimulation of the tissues by peptone broth as has been worked out by Friedländer and Tooney.[5]

We have in mind merely to report a summary of results in certain groups of cases without attempting to say exactly which of the above possibilities is responsible except to say that the last, that of Friedländer and Tooney, could not have been the *sole* cause of the marked improvement so often observed. We treated several cases with peptone broth and saw some improvement, as might be expected, but never observed striking effects.

Boils and Carbuncles. Sixty-six cases treated, with excellent results in 55, intermediate results in 5, failure in 5, and no report in 1. At least 4 of the failures may probably be explained by the fact that the organism responsible (streptococcus in 2 and resistant staphylococcus in 2) was not susceptible to the bacteriophage strains at our disposal, as was determined by tests *in vitro*. In other cases with relatively unsatisfactory results the lesions were so deep that local application of the filtrate could not reach the site of the actual infection. Permission to inject was not granted.

We have had 10 cases of generalized furunculosis of extreme grade —fifty to three hundred and fifty boils present simultaneously in each case—in children from five months to ten years of age. All of these have shown spectacular improvement immediately after the application of the bacteriophage. Most of these children were in bad condition when we began treatment—emaciated, badly nourished, running considerable temperature, extremely uncomfortable, and in several instances considered to be critically ill. The bacteriophage was applied directly as a wet dressing, or in several instances injected directly into the lesions with a fine needle. In every case except one the child was markedly improved the following day, the temperature was lower, the pain and soreness less, the early boils tending to abort, the older ones moving rapidly toward liquefaction, and the child apparently turned toward recovery.

Several carbuncles have been promptly helped in a striking way. Boils in the nose and external ear canal have usually been less painful and have rapidly come to a head when treated with pledgets of absorbent cotton wet with the filtrate and changed every hour or so. Particularly desirable is the fact that these very painful and even dangerous boils may be treated effectively by this method without manipulation that may cause them to spread. Stye in a few cases has responded nicely. Several of our patients with boils have been diabetics, and have shown good results except that the lesions have possibly been a little slower to close.

Patients with "crops" of boils have usually obtained relief from the effects of the particular lesions, but in only about half of the cases has the attack entirely stopped. Bacteriophage does not always immunize the individual against subsequent boils though it

has sometimes apparently done so. We have in mind perhaps a dozen individuals who have continued to have boils but have controlled them quite easily when they have appeared.

Superficial or opened boils have simply been treated with a wet dressing of the filtrate; deep lesions have been injected, or treated with a wet dressing after having had the skin broken with a needle or scalpel. In some cases we have applied the bacteriophage suspended in a 1 per cent agar jelly. In nearly all cases there has been a marked diminution in the pain and soreness, the necrotic core has liquefied rapidly and has easily come out leaving a clean crater which has healed in the minimum time. Frequently the relief has been surprisingly prompt. Early boils have frequently been aborted. We have not injected bacteriophage into the arm as is advocated by Larkum[6] and many others; nor have we used the filtrate as one would use a vaccine as recommended by Arnold and Weiss.[3]

A large number of workers have used Staphylococcus bacteriophage in the treatment of boils and related lesions. Bruynoghe and Maisin[7] seem to have been the first (1921) to report favorable results in furunculosis. Gratia,[8] the discoverer of the highly potent strain which bears his name, reported soon after (1922) favorable results in a wide variety of staphylococcus conditions. Gougerot and Peyre,[9] in 1924, got favorable results in staphylococcus lesions. More recently Hauduroy, Camus and Dalsace,[10] Hauduroy,[11] Rice,[12] Grenet and Isaac-Georges,[13] Larkum,[6] Lingeman[14] and others report favorably.

Abscesses. Twenty-seven cases; 24 are reported as having shown excellent results, 1 intermediate, 1 no improvement, the primary condition having been hopeless and 1 no report. If the abscess had been opened as was usually the case, the phage was simply instilled or injected into the cavity by means that seemed appropriate at the time. We have commonly anchored a catheter in deep lesions and have then injected the filtrate with a glass syringe into the open end of the tube. Recently we have injected the filtrate suspended in a 1 per cent agar jelly when the cavity was in such position as to allow the liquid filtrate easily to leak out. Such an agar preparation readily passes through a syringe and has given particularly good results. The attendant should be warned not to be alarmed by the appearance of the agar as it may come from the abscess cavity.

Many of the abscesses treated were of months' duration, and a few had been draining for years. A sinus and abscess of seven years' duration having not once been closed in that time, healed completely in three weeks and has since remained sound. A large chronic abscess at the site of a nephrectomy operation done several years before was 6 inches deep and had a capacity of more than 100 cc. by accurate determination. The patient's color was bad, he had considerable temperature, was badly emaciated, and otherwise in an unsatisfactory condition. After the injection of bacteriophage into

the cavity he showed prompt improvement, the wound closed completely, and he gained 22 pounds in an interval of five weeks.

Particularly good results were obtained in these cases in which the abscess had not been opened when we first saw the patient. The filtrate was injected through a fine needle directly into the cavity, or into the badly inflamed tissues about it. The injection was repeated until the area became markedly fluctuant, and the soreness and signs of local inflammation had abated. When this state had been reached, the abscess was opened with the smallest incision that would serve the purpose of draining the highly fluid pus. The lesions have then healed with the rapidity of a surgical incision. There may seem to be some objection (as judged by past standards) to the closed treatment of an abscess after it is evident that it contains fluid pus, but there can be no danger when the temperature and the signs of local reaction have abated as has been rather uniformly observed. The closed method has the advantage that secondary infection of the abscess is avoided, the smallest possible amount of bacteriophage need be used, and there is decreased danger of spreading the infection when the well-localized abscess is opened.

Staphylococcus Cellulitis. In addition to the above cases of abscess, may be mentioned five others of Staphylococcus cellulitis of marked grade, which were all treated successfully with phage after other means had failed. All of these lesions were large, extremely painful, causing considerable temperature, and stubbornly refusing to localize and liquefy. Three of the patients were considered by clinicians to be critically ill. Bacteriophage was injected in several places into the board-like tissues—usually about 0.5 cc. being used in each place. Needless to say this is a painful procedure, but may be relieved by the use of gas or other short anesthetic. The pain of injection, being due to increased tension, is, at the worst, of but a few minutes' duration, and is followed by marked relief.

The rate at which these lesions came to suppuration, and later to healing, was uniformly surprising. In each instance, the patient rested well the following night after having had little rest for days or even as long as three weeks before. The following day considerable pus was present, but was not released until highly fluid and sharply localized. Studies by Nelson[15] and by Smith[16] have shown that bacteriophage filtrates have great power to promote phagocytosis of the homologous organism. Hadley[4] points out in his splendid review of the literature on microbic dissociation that bacteriophage in one of the very best means of causing a culture of bacteria to turn "rough" and that when rough the organisms are much less pathogenic, and much more susceptible to phagocytosis. This doubtless explains the rapid suppuration and the prompt liquefaction of the necrotic material in the abscess cavity. We have commonly observed a marked increase in pus production on the day following the application of the phage. This is regarded by us as an omen of great

promise inasmuch as it means that the reagent is active against the particular lesion being treated.

We have often been struck by the vividness of the description of the results of various experimenters, and until we had had personal experience were much inclined to be skeptical of them. We have, however, been able to verify these findings repeatedly. McKinley,[17] Hauduroy[10,11] and others give glowing accounts of the prompt relief of pain and rapid return of function. To be sure Besredka[2] describes exactly the same results following the use of his antivirus (filtrates of old staphylococcus cultures). Bazy[18] ascribes the good results to the presence of the soluble products of the lysed bacteria, and doubts if the bacteriophage has much to do with it except to cause the lysis. Arnold and Weiss[3] emphasize the importance of the highly available antigen that is produced by the solution of the bacterial substance.

Staphylococcus Purulent Arthritis. Four cases (nine different joints); excellent results in all. The phage was injected directly into the involved joint cavity after pus-containing Staphylococcus aureus had been aspirated. In every joint there was improvement, and in nearly every one there was restoration of complete function (observation of Dr. Garceau, resident of Riley Memorial Hospital, Indiana University). One of the children died subsequently of another condition. At autopsy the two shoulder-joints, both of which had been seriously involved, filled with pus and injected with bacteriophage, were found to be in normal condition and had given perfect function for weeks before the death occurred.

Appendiceal Abscess. Seventeen cases; 14 excellent results, 2 good and 1 failure. The failure was a child that was evidently moribund from advanced general peritonitis. Death occurred a few hours after the child was first seen by us. The phage was only put into the opening of the abscess since permission was not granted to inject it into the peritoneal cavity. In all of these cases a mixed Bacillus coli-Staphylococcus bacteriophage was used. We repeatedly saw rapid healing of the lesion even though the tissues were covered with fecal material from the bowel. One of these cases was described at a county medical meeting as being quite hopeless. Several members of the society agreed that the child would in all probability die in a few days. She was in coma-delirium, temperature high, abscess very foul, and showing much fecal drainage. The day after phage was started she was definitely better for the first time, and continued rapidly to complete recovery.

Peritonitis. Three cases, all desperate, have been treated, not counting the one mentioned just above. Two are now alive and well. The third died of acute heart failure several weeks after the height of the infection. This man seemed well along toward recovery after a desperately stormy course, but was found at autopsy to have several deep abscesses which had not been found and treated *antemortem*. The filtrate (mixed coli-staph) in these cases was

instilled into the laparotomy wounds. It was, of course, impossible to say how far it penetrated or how it acted in relation to the peritoneum. All of these cases received every other good treatment that the staff could devise. We believe that bacteriophage was but one of half a dozen agents which helped in the results. Inasmuch as it was the only *new* factor in the therapy, we feel that it was a distinct and valuable contribution. These patients were extremely ill and it is likely that failure on the part of any one of the remedial measures would have precipitated disaster.

Puerperal Sepsis. Our one case was desperately ill when she was brought to the University Hospital. As a last resort the attending physician suggested injecting bacteriophage (coli-staph) directly into the cavity of the infected uterus through a sterile catheter. The condition of the patient seemed to justify this dangerous procedure. Injection was made several times during the next two days. The temperature fell rapidly beginning a few hours after phage was begun, and the clinical condition improved. Treatment of so unusual character seemed no longer indicated and the injections were discontinued. The patient recovered, but it was impossible to say whether phage was the real cause or may have been used coincidentally with spontaneous improvement.

Fecal Fistulæ. Four cases with infected fecal fistulæ have been treated with cure in 2 and failure in 2. One of the later died of the primary condition before time enough had elapsed for the phage to have had a fair trial. The other was a child in a critical condition from tuberculous peritonitis with fecal fistula and marked secondary infection—usually considered to be a hopeless combination.

One of our recoveries was probably our most striking case. A young woman had a condition diagnosed by many different physicians as tuberculous peritonitis with fecal fistula. The diagnosis was confirmed early in the course by a surgeon with the abdomen open. When first seen by us she had been ill for something over a year, and no one had given her the least hope of recovery. At the time she was running a temperature of 103° to 104° F., was comatose or in delirium all of the time, was extremely emaciated as a result of the infection and the inability to eat or retain food except in very small amounts. All of the bowel contents were coming from the fistula, which was evidently high. She was being given as many as three intravenous dextrose injections daily. About the opening of the fistula there was a deep ulcerated area about 5 inches in diameter, and undermined most of the way around as much as 3 inches. A wide variety of therapeutic agents had been used without success; she had grown progressively worse, and was to be sent home because nothing could be done. At this time we began instilling mixed bacteriophage (coli-staph) into the ulcer and fistula. In a week there was definite improvement as shown by lower temperatue, less

odor, and a better general appearance. After several months of practically constant improvement she went home well, weighing 122 pounds (normal weight for one of her height, 119). During the next four months she did washing, ironing, cooking and cleaning for a family of eight, and has now for several months worked fifty-five to sixty hours a week in a laundry. When last seen the lesion was entirely closed, she weighed 142 pounds, and appeared to be in the best of health.

Possibly this was not a case of tuberculous peritonitis though the diagnosis was made at the time of the abdominal operation, was repeatedly confirmed, and never questioned until the patient was nearly well. Bacteriophage, of course, had no effect upon the tuberculosis as such. The effect could only have been that of controlling the secondary infection—a most important matter in tuberculosis. If this was tuberculous peritonitis it was one of the extremely few who get well after the complication of serious secondary infection and fecal fistula has developed.

Urinary Fistulæ. Five cases; 2 excellent results, 2 that were good and 1 that was poor. In all of the cases the characteristic pus discharge was checked and the lesion became clean or relatively so.

In 2 cases the tract became clean but would not close. It is likely that epithelium had grown into the fistulous canal making closure impossible. The nature of the lesions made it difficult to destroy the epithelium.

Cystitis. Three cases gave excellent results. The coli-staphylococcus mixed phage was instilled into the bladder and retained as long as possible. We obtained no such spectacular results as are reported by Frisch,[19] but were well pleased. Another case not treated was of particular interest. A woman had been suffering from a severe cystitis, and a specimen of urine was sent to the laboratory for isolation of the causative organism and the preparation of a specific phage against it. After three days the filtrate was ready, but was never used for the reason that the patient had suddenly improved markedly. Another specimen of urine taken after the improvement was found to contain a strong lytic agent against the organism isolated before. This woman had developed her own bacteriophage before we were able to get the laboratory strain ready for her. This case illustrates the need of a stock preparation.

Due probably to the fact that d'Herelle worked first with a related organism (Bacillus dysenteriæ) and that Bacillus coli itself is very easily lysed by strains that can be picked up nearly anywere, infections of the bladder and urinary tract by the coli organism have early and frequently attracted the efforts of investigators of the possibility of phage therapy. A number of workers have reported success, or have made interesting observations concerning the spontaneous development of active bacteriophage strains in cases that

were recovering from various infections of the urinary tract. Prominent among these may be mentioned Beckerich and Hauduroy,[20] Larkum,[21] Ravina,[22] Zdansky,[23] Caldwell,[24] Dalsace,[25] Dutton,[26] Philibert,[27] Winans.[28] Cowie[29] reports sterilization of the urinary tract when the phage was given subcutaneously, while most of the other investigators have used it by instillation into the urinary tract. Walker[30] in a recent article shows that Bacillus coli phage is able to protect mice against large doses of Bacillus coli injected intraperitoneally.

Infected Wounds. Forty-four cases; 40 excellent results, 3 good, no effect in 1. There was no apparent reason for failure in the 1 case. The wound contained a staphylococcus which was susceptible to our phage, but it is possible that this was but a secondary invader, and that the real etiologic agent was something else. This was true of 2 other cases not counted above. In each of the latter there were multiple lesions not at all helped by the filtrate. One was found to be due to a yeast infection (monilia) and the other to broken down gummata. For obvious reasons, these 2 cases are not regarded as being suitable for phage therapy and were not counted in the 44 cases.

Very commonly the wounds increased in their pus production for the first twenty-four to thirty-six hours after the first application, but after that they were cleaner, and rapidly developed a healthy granulation tissue. Some patients reported that the liquid caused an intense burning sensation lasting for a few minutes. After this period, however, it was quite soothing. Some found it soothing from the first. Both of these responses were found to presage a favorable result. When the patient experienced neither the burning nor the soothing sensation, the result was likely to be slower or not so good.

Probably as a result of the rapid healing usually observed we have in several instances found the scar remaining to be quite soft and pliable.

Bed Sores. Twenty-one cases; excellent results in 15, good in 2, poor in 1, and in 3 the patient died of the primary condition before there had been time enough for a real trial of the phage. The failure was a boy with several large sores on his completely paralyzed legs. The same number of sores on his back did very much better. We are inclined to think that the failure to close was due to the fact that the tissues were unable to regenerate due to the trophic disturbances which were evidently present. The sores have remained clean or nearly so while the phage has been used.

In reporting that 15 cases gave excellent results we do not mean that all were entirely healed. If the lesion became clean, was granulating, and starting to close in a badly debilitated patient, we have considered the result excellent. Phage can only control the infection with Bacillus coli and staphylococcus which is always present in

these bed sores. If the patient's vitality is too low to furnish the actual healing, or if the condition which caused the sore in the first place still exists it is unreasonable to expect complete closure.

Among our patients there were 3 with broken backs. The enormous sores so commonly seen in such cases were in an advanced condition, but all became clean and were closing when death occurred. In one there were multiple lesions varying from 1 to 5 inches in diameter. Those under 2 inches were completely healed and there was a wide rim of new skin about the larger ones, when the patient died. A recent patient in his seventh decade has syphilis and arteriosclerosis of such grade that both legs were gangrenous (and later amputated below the knee) because of the failure of circulation. This man had two deep bed sores over the sacrum. Both became clean and closed completely though they were very slow at the end. The peripheral circulation in this man was so poor that a good result could hardly be expected. Another old man, aged sixty-nine years, had a large prostate, residual urine, cystitis, paraurethral abscess, suprapubic cystotomy wound, septic temperature and two bed sores (one was 4 inches in diameter and the other 2 by 4 inches). We were given the case at the same time that his people were notified that he could live but a short time. He made a complete recovery, beginning to show improvement within twenty-four hours after the first application of the filtrate. A year later he came back to have the large prostate removed and the suprapubic opening closed. At this time he was found to be in good physical condition, and the scars where the two bed sores had been could hardly be distinguished from the neighboring skin.

All of our patients with bed sores were, of course, given the very best general treatment available, but no other medication was used on the sores except that in a few instances Balsam of Peru was used after the sore was clean—and if the proliferation of epithelium seemed in need of stimulation. In several instances we saw the wound healing in a satisfactory way while the general condition of the patient was getting worse. In practically every case phage has checked the offensive odor that makes bed sores such a trial to the family and the nursing staff. This is an achievement of considerable value even if nothing else comes of the treatment. One patient dying of tuberculous meningitis had four enormous bed sores. The two worst ones were treated with phage, the other two according to the hospital routine. A week later the man died, and it was found that the two sores treated with phage were decidedly cleaner and healthier in appearance. This is not in accord with the usual theory that phage spreads rapidly to remote parts.

Leg Ulcers. Three cases; 2 excellent results and 1 good result. Two of these cases had been put to bed, and it is not impossible that this is the cause of the good result. In both cases, however, they had already had bed rest, and the patients were sure that the

improvement was more marked after the filtrate was used. As in the case of bed sores, the phage can do no more than help control the infection that is present. Obviously it cannot correct vasomotor or trophic nerve disturbances. Bizard, Marceau and Rosenthal[31] report successful treatment of ulcers of the leg with phage.

Perineal Lacerations. Ten cases; results excellent in all. The phage was used as a prophylactic in cases that were handled in the most carefully aseptic manner. The lacerations were repaired in the usual way, and then bacteriophage was allowed to run over the stitches, being applied three times a day as a rule. In all there was rapid healing without pus or evidence of inflammation. Probably all would have done well without phage, but it seemed as if these cases did particularly well (opinion of Dr. Bedwell, resident of Coleman Hospital). Three of the patients had third-degree tears (involving the rectum) and were certainly contaminated. One of these women had a normal bowel movement without aid on the eighth day and went home on the ninth.

Osteomyelitis. Eleven cases; 4 excellent results, 3 fair, and 4 no effect. Our general impression is that in osteomyelitis the value of phage is less than would be indicated by these figures. If there is dead bone in the lesion it has apparently little or no value. When all necrotic bone has been removed, we have obtained good results, but under such circumstances the result may have been good without phage. In this connection it is interesting to note that Albee[32] has a theory that the efficacy of the Orr closed treatment for osteomyelitis is merely a means of causing the patient to develop his own bacteriophage. If this view is correct it should be possible to find the active phage in pus from such lesions when the case is removed. We are at present testing this point in a series of cases, but are not ready to report.

Infected Tuberculous Lesions of Bone. Two cases were attempted; both were failures. It was hoped that we might be able to control the secondary infection and in that case the bone might be able to overcome the tuberculous process. Both were treated for several weeks with no evident improvement. It is likely that there was dead bone in each.

Mastoidectomy Wounds and Running Ears. Nine cases; 6 excellent results, 2 good and 1 failure. If there is dead bone in the mastoid region, failure may be expected. Several of these cases had been running for years, and were dry and odorless for the first time in months within a week or ten days after phage was used. We were not able to ascertain whether the condition returned at a later date in these cases.

Sinusitis. It is almost impossible to estimate the results in these cases inasmuch, as we mostly had to depend upon the patient's description of his feelings. In several instances we have felt that our friends were trying to please us by reporting that they thought

they were "some better." Since the tendency of an acute attack is to improve, it is likely that some of our "cures" were spontaneous. Furthermore, a considerable number of our cases treated for this condition have not returned to report or to continue treatment. A few have had surgical conditions in the nose that would make any sort of medical treatment futile.

We have, however, had some results that were decidedly gratifying, and are responsible for our intention to continue the work further. A prominent physician who has had serious sinus trouble for years reports that he is much pleased with results in his own case, and is emphatic in his insistence that we continue. Inasmuch as he has had a static condition for a long time and is well informed on the subject, we are inclined to give ear to his opinion. A few cases have had Roentgen ray examinations before and after, which seem to show improvement. Two very bad cases have been able to remain during the winter in our irritating climate, while heretofore they had found it necessary to go to the southwest during that season. In all we have had 15 cases that have given the phage a fair trial. In 7 we have thought the results excellent; in 4 good; and in 4 there have been failure. If every case seen were reported, the number of failures would be greater, but we have only counted such cases as continued the treatment long enough to make it reasonable to expect something.

The difficulties are several in this work. In the first place, it is hard to know with certainty that one has the right organism; the filtrate is hard to apply; and finally it is sometimes impossible to evaluate the results with accuracy. Most of the cases have been treated with phage developed from autogenous cultures. Several patients have found the filtrate quite irritating, but this is not unlikely, partly or entirely, due to a lack of isotonicity—a point to be corrected in the future. We have a rumor that a patient using a stock preparation, not under our supervision, had an allergic reaction of acute nature after dropping the filtrate into his nose.

There is much to be done in connection with the use of bacteriophage in the treatment of sinus infections, but we have seen results sufficient to encourage us to go ahead with it. Schumm and Cook[33] report negative results in the main, but there is some reason to criticize their methods. Hayes[34] reports that he has had good results with the use of Besredka's antivirus in sinus infections. He used it in essentially the same way that we have used our filtrates. It is not impossible that our results have been due to the antivirus action, or it may be that Hayes had a spontaneously developed phage in his old broth cultures. It is unnecessary to remind the reader that a reagent that would really cure even a small percentage of chronic sinuses would be a great success.

Staphylococcus Septicemia. Two cases. In each case the patient died, as was to have been expected after the blood had been

found repeatedly positive for staphylococcus. One of the cases was moribund when we began, the other lived for weeks longer than was expected, and it was thought that this may have been due to the effect of the phage. The filtrate was not injected intravenously in either case as we were afraid of the effects of the peptone broth. Open lesions in the cases were treated and subcutaneous injections were made. Dutton[35] reports that he has seen several recoveries believed due to phage.

Impetigo. Three cases treated and all did well. One bad case served as a control. One side was treated with phage and the other with ammoniated mercury ointment. Both sides were kept clean in the same manner. The phage side did considerably better.

There are those who believe that the initial etiologic agent in impetigo is a streptococcus, but even so staphylococcus is practically always found as a secondary invader. Staphylococcus phage was used in all of our cases.

Acne. Thirty-five cases; 13 excellent results, 8 fair, 7 no effect, 7 did not return. In the main we have had excellent results in the severe cases with much pus in the skin; fair results in the moderate cases; and no good effect in mild cases. Unfortunately for our purpose it seems that every one who cares enough to come to us for treatment, seems to think his or her case is one of unusual severity. We now refuse treatment in any but markedly pustular cases. Several young people with badly involved faces are now entirely free except possibly for the scars. The pimples become less sore and red, and the face less indurated. In half a dozen cases we have been able to get large amounts of pus from a face that two or three days before was indurated, red and sore. In such instances there was prompt relief. Commonly we have found the skin of our acne cases to be very oily, and after the inflammation has been relieved have recommended Roentgen ray treatments for the condition in the hope that this would prevent recurrence.

In treating acne we have had the patient wash the face with hot water and rather strong soap twice a day. He has then been instructed to open pustules and press out the contents, later wiping the face thoroughly with an alcohol sponge. When the face was dry the phage (Staphylococcus aureus and albus) suspended in a 1 per cent agar jelly was rubbed into the skin and allowed to remain. It soon disappeared leaving nothing to indicate its presence. Treatment for acne has by no means been a complete success, but we are reminded that no other treatment is such by a very great deal. Most of our cases had "tried everything" before we saw them. A medical student with 30 to 40 ugly pustules all of the time showed prompt improvement, and was entirely well in about a month. He now has an unusually clear skin. No attempt to find a phage active against Bacillus acne has been made inasmuch as we have believed that it was of no real consequence in the causation of the condition.

Streptococcus Infections. No attempt has been made by us, as yet, to develop a Streptococcus phage, but in 5 or 6 cases we have begun treatment under the impression that we were dealing with a staphylococcus and have had a good result, later to find that streptococcus was at fault. In at least three of these the phage used was found to be active against the organism. In all the streptococcus was nonhemolytic, and the lesion well localized. In 2 cases of acute streptococcus boils, the Staphylococcus bacteriophage was of no avail. Some of our strains of bacteriophage have been found to be active against certain cultures of streptococcus and pneumococcus *in vitro*. Other investigators have reported good results from the use of Staphylococcus bacteriophage in streptococcus infections as may be mentioned, Dutton[35] and Hadley[4] who refers to the opinion of Larkum and of Pryor. Dutton[36] reports good results with the use of what may be a Streptococcus bacteriophage but is not typical. The great number of strains of streptococcus makes the problem one of particular difficulty.

General Discussion. In our opinion bacteriophage therapy is a distinct and valuable contribution to the armamentarium of the physician and surgeon for the treatment of suppurative lesions. It is not a cure-all by any means and the note of warning sounded by the editorial[37] in the *Journal of the American Medical Association* is well taken.

In suitable types of infections it may be expected to do certain things which in our opinion cannot be so well done by any other known remedy. Experience is necessary, of course, in applying it so as to get the best results without waste; in knowing when to apply it; and in evaluating the results. Particularly is it important that the physician and the patient be warned that the first twenty-four to thirty-six hours may show a distinct increase in the amount of pus. This is a good sign. Dosage does not seem to be important except that enough must be used to give good contact with the reagent. As a rule we have used larger amounts than the practising physician would feel justified in using because of the expense. Frequent administrations or dressings with it have seemed to give the best results.

We have been anxious to make the preparation available to the profession, knowing that it could be of little use if it must be prepared for each case separately. Most of the last 250 cases have been treated with a stock preparation, the greater part of which has been made under our direction by the Swan-Myers Company of Indianapolis. This company has furnished, without charge, large amounts of the various preparations for the purpose of making a clinical test under conditions as nearly as possible like those in actual practice. The stock preparations have seemed to be just as good, except in a very few instances, as the phage prepared by the laboratory for a particular patient.

In the beginning of our clinical work we would accept for treatment only those cases that were considered by the staff or the physician-in-charge to be in a hopeless condition, and on which permission was granted to stop all other therapy. There are at present 30 or 40 of these people alive and well. A considerable number of our patients are dead of their original condition though the lesion treated with phage was well at the time of death. A rather large percentage of our cases which turned out favorably were complicated by diabetes mellitus, syphilis, malnutrition, old age, inanition, arteriosclerosis, trophic nerve disturbances or other processes well known to retard healing.

With the exception of the report of the allergic distress following instillation of the phage into the nose, the burning sensation which lasts for but a few minutes in some cases when put on raw wounds, and two or three moderate chills within a few hours of the application, we have seen or heard of no bad results. A number of investigators have been afraid that there might be developed in the patient a strain of phage-resistant organisms which would be more pathogenic than the original. We have seen absolutely no evidence of such a phenomenon, and feel that when phage is applied locally there is no danger of such a result.

Conclusions. 1. In about 90 per cent of cases we have had excellent results with the local application of bacteriophage filtrates (Bacillus coli, and various strain of Staphylococcus aureus and albus) to suppurative lesions due to the homologous organisms.

2. Our experience does not inform us as to the manner in which the reagent acts except that we see evidence of increased phagocytosis and liquefaction.

3. Stock preparations are apparently as good as those specially prepared except in a few cases. Stock preparations have the great advantage in that they are readily available at the time needed, and can be used at a distance from a bacteriophage laboratory.

4. We have seen little or no evidence that the treatment of one lesion or the injection of the phage into an uninflamed area will influence a distant lesion except when there is actual contact with the reagent. We have, however, made very little attempt to study this relation.

5. Dosage does not seem to be important, provided the filtrate is used in sufficient amount to give good contact as a wet dressing.

6. No bad results of importance have been observed. There has been no clinical evidence of the development of resistant strains that were more pathogenic than the original.

7. Bacteriophage therapy should be regarded as an addition to the armamentarium of the physician rather than as a substitute for something already used.

8. Strong antiseptics have seemed to be contraindicated while

phage was being used, but we have no experience to tell us that they would have altered the results.

NOTE.—We must take this opportunity to express our thanks to the large number of clinicians who have coöperated with us and have made this work possible. Particularly have we to thank the staff of the Indiana University Hospitals for their interest and advice.

Readers interested in general discussions of bacteriophagy, and in complete bibliographies are referred to works by d'Herelle,[1] and Hadley.[4]

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THREE METHODS OF OBTAINING INTESTINAL MATERIAL DIRECTLY FOR BACTERIOLOGIC EXAMINATION WITHOUT THE POSSIBILITY OF CONTAMINATION FROM SURROUNDING SOURCES.

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In the investigation of certain phases of the bacterial flora of the human intestine in living subjects in health and in disease, we were impressed early by the difficulties encountered in securing contents, secretion or excretion from a definite source or location within, and directly from, the intestinal tract without contamination from continuous and contiguous areas. The antomy of the intestine and our present nonoperative methods of exposure of the part desired for the obtaining of material are such that we do not believe that the probability of contamination from near and adjacent sources has been overcome by present methods.

In recent years the use of the proctoscope and sigmoidoscope has been extended from inspection and treatment of gross bowel lesions to their use in protozoal[1] and bacteriologic investigations of the distal colon[2] because of the advantages of employing fresh material from direct sources. In the application of this method, as well as in the securing of intestinal material through fistulous openings, sterile cotton swabs on long wooden applicators are usually employed. The difficulties encountered in their use in an attempt to secure uncontaminated material for bacteriologic examination are as follows:

The size of the lumen of the distal intestine afforded by the introduction of a proctoscope or sigmoidoscope is limited. This makes it more often impossible to introduce and withdraw through the instrument without contamination from near and adjacent areas, an applicator of the type usually employed and mentioned above. Also, and again because of the relative smallness of the lumen, one often unavoidably touches with the applicator the distal portion of the proctoscope or sigmoidoscope which frequently contains, even in the presence of an apparently grossly clean intestine, some content or secretion as a result of insertion, advancement and manipulation of the instrument in the intestine.

In order to obviate these dangers of contamination, inherent in both the near and adjacent tissue of a restricted intestinal segment, as well as in the distal portion of the proctoscope or sigmoidoscope,

the following devices have been developed. These may be used separately or jointly depending on both the wishes of the worker and the case at hand. They enable one to secure a sufficient quantity of intestinal material for bacteriologic study which we think can be regarded as representing the true material from the source desired uncontaminated by material from surrounding areas.

1. The first device consists of 7 to 8 mm. soft laboratory glass tubing in three lengths: 8 cm., 17 cm. and 30 cm. Permitting free motion within the glass tube is a cotton swab attached distally to the roughened end of a firm iron wire applicator of 16 gauge. The iron wire applicator is about 12 cm. longer than the length of the glass tubing which encloses it. The increase in length of the iron wire over that of the tubing is the length of that part of the applicator which extends proximally beyond the tubing. This extension is used for two purposes: (1) to make a small handle (Fig. 1), and (2) to permit projection of the applicator for about 8 cm. beyond the distal portion of the glass tube when the device is in use (Fig. 3).

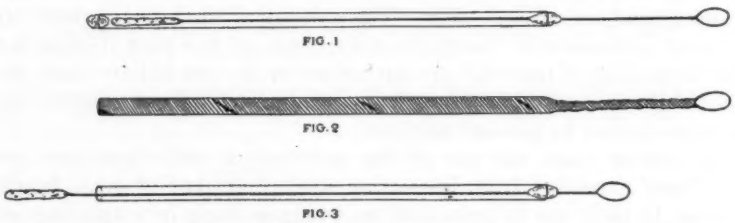

FIG. 1

FIG. 2

FIG. 3

FIG. 1.—Shows one size of the type device used in the first and third methods completely assembled. After use, the device would appear as in Fig. 3 but without the distal cotton pledget.

FIG. 2.—Shows the device wrapped prior and subsequent to sterilization.

FIG. 3.—Shows the device in use: the projection of the swab beyond the glass tube which protects it from coming into contact with the proctoscope or sigmoidscope, and from surrounding tissue and sources.

In further preparation, a small pledget of raw cotton is placed at each of the two ends of the glass tube so as to keep the applicator from slipping out at the distal end and to fix it to the tube at the proximal end. The device now being completely assembled (Fig. 1), next is wrapped in paper save for the handle which projects beyond it (Fig. 2). It is sterilized, then, in the autoclave. These tubes may be prepared in quantity in the several sizes and used as desired.

With the proctoscope or sigmoidoscope in place, and if necessary held there with the aid of an assistant, the paper covering now is removed from the sterilized device. Next the distal cotton pledget is withdrawn, the distal end of the device is passed quickly through a flame, and then the device is inserted through the instrument *under the direct vision* of the worker to a point directly over, but not touching the area from which the material is desired. Still

under the vision of the worker, the applicator is pushed forward and the swab now is in contact with the sought for involvement; then, with the glass tube in its original position with relation to the involvement and instrument, the applicator is drawn back into it and only then is the entire device withdrawn from the proctoscope or sigmoidoscope. Care should be taken that the distal portion of the glass container should touch neither the intestine nor any of the contents. As soon as possible thereafter, and immediately subsequent to the flaming of the proximal end of the device, the material-containing swab is removed through the proximal portion of the glass tube so as not to touch the distal end again. The swab is placed now either in a sterile test tube, or the appropriate media are directly inoculated.

By means of this glass tube which encloses the iron wire applicator and cotton swab, the working area through the instrument and within the bowel is much reduced, thus protecting the swab from coming into contact with any of the region surrounding the point from which material is secured, and also from being contaminated by contact with any part of the proctoscope or sigmoidoscope. The 17-cm. long tube is employed when the proctoscope is used; the 30-cm. long tubing, when the sigmoidoscope is used. The 8-cm. length, for securing material directly from the intestine through a fistula, will be discussed later.

2. The second procedure is one which permits the obtaining of contents, secretion or excretion for bacteriologic study, directly from the lower sigmoid through a sigmoidoscope, without contamination either by rectal contents or from other sources. It is a modification of the method described by Andrews and myself for the detection of protozoa from sigmoid contents.[1] The method is as follows:

The patient is placed in Haynes' position, that is, the lower extremities remain on the table, while the trunk, flexed at the hips, is virtually at right angles to the lower extremities; the head rests on the forearms, which are flexed at the elbows and are supported by a footstool of convenient height. This position has been found preferable to the usual, well-known, knee-chest posture. In the Haynes' position the viscera are, by force of gravity, moved out of the pelvis, up toward and against the diaphragm. This reduces intrapelvic pressure and facilitates both instrumentation and the proper execution of this method.

Next, the anus is cleansed, first with green soap and water, then with alcohol if desired, and finally with a 1 to 1000 solution of bichlorid of mercury. The right hand is now covered with a sterile glove, the first finger of which is inserted into the rectum so as to stretch the anal sphincter to render more easy the inserting of the sigmoidoscope, if for no other purpose. The sterile sigmoidoscope, covered with a sterile lubricant, next is inserted. The patient is

ordered to take neither purge nor enema prior to this examination, because we learned that any method which results in the thorough cleansing of the rectum will also result in a clean sigmoid with no gross material available for study at either point. If this is done, he usually appears with feces in the rectum. In order to pass from the rectum into the sigmoid so as to secure material from the latter point without contamination from the former source, the subsequent steps are pursued:

With the instrument in the rectum near the feces encountered, the rectal content, diluted when necessary with sterile saline introduced into the sigmoidoscope through a sterile funnel placed in its proximal end, is drawn out through a sterile aspirator 35 cm. by 8 mm., by means of a suction apparatus. In this way the rectal feces is removed without affecting the material in the sigmoid. When the sigmoid is entered, the type applicator described above may be employed to secure through the sigmoidoscope the material desired without contamination from surrounding sources.

Distally lighted instruments are to be used in the execution of methods 1 and 2. The proctoscope and sigmoidoscope used by us, each present a diameter of 16 mm., a diameter no greater than that of the average adult male index finger. An instrument, the diameter of which is as low as 12 to 13 mm., can be used in this work when necessary; however, the former size is to be preferred.

3. The securing of material for bacteriologic study directly from the intestine through a fistula is accomplished by using the iron wire applicator enclosed in a glass tube 8 cms. long. In this case, the paper wrapper having been removed, the sterilized device is inserted, not necessarily completely, directly into the fistula. Excepting that the subsequent steps cannot be performed in their entirety under the direct vision of the worker, they are, however, identical with those described for Method 1. The use of this type applicator in an intestinal fistula presents the advantage of not only preventing the swab from touching the protruding mucosa or adjacent skin, but also keeps the swab from coming into contact with the mucosa of the intestine beyond the fistulous opening upon entry and withdrawal. The contraindications to the use of this device are a fistulous opening too small to permit its entry into the intestinal lumen, and many appendicostomies in which both the opening and appendiceal lumen are too small.

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INTESTINAL PERMEABILITY IN OBSTRUCTION OF THE COLON: AN EXPERIMENTAL STUDY.*

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Surgical experience has taught the wisdom of avoiding undue operative manipulation of the distended colon proximal to an obstructed area. It is said that mere handling of the obstructed bowel may cause peritonitis because of the greater permeability of the distended intestine. Our investigation was made to determine whether or not such increased permeability could be demonstrated experimentally.

Early investigations of the permeability of the wall of the bowel for bacteria were concerned mostly with cultures taken from the peritoneal surface, and the blood, after obstruction had been produced. Helmberger and Martina[4] reviewed the literature up to 1904. The results of cultures in cases of strangulated hernia and in animal experimentation were very contradictory. On the basis of their own observations on rabbits they concluded that the obstructed bowel is permeable for bacteria only in the presence of definite necrosis, and that the muscular layers offer more resistance to bacteria than the other layers. Garnier and Simon[3] also found that positive results from culture of the blood in intestinal obstruction depended on the presence of ulceration. In summarizing the literature up to 1923, Rost[8] said that in experiments to determine the penetration of the intact intestinal wall by bacteria the organisms had been demonstrated only occasionally, and that it was necessary to injure the intestinal wall rather severely before positive results could be obtained from cultures made from the peritoneal surface. Clinical and necropsy observations, however, have been reported of peritonitis which probably arose through penetration of diseased intestinal mucosa, such as occurs in severe enteritis. Aside from the question of bacterial penetration Brooks and his associates[2] have presented evidence to show that even the toxic element in the content of an obstructed loop is not absorbed unless some circulatory interference has injured the mucosa. Stone and Firor[9] reported experiments in which they concluded that the raised intraintestinal pressure in obstruction is the cause of abnormal absorption. They injected India ink into the normal small intestine, into the intestine

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partially obstructed by a ligature, and into a loop completely occluded by a ligature at either end. Absorption did not take place under the first two conditions, but in the dogs with completely occluded loops the mesenteric lymph nodes were found to be black. These dogs, however, recovered because the ligature cut through. The injury, incident to this, rather than increased pressure during temporary complete obstruction might well be the cause of the abnormal penetration of the wall of the bowel. That intraintestinal pressure is definitely increased in obstruction has recently been shown experimentally by Owings, McIntosh, Stone and Weinberg.[7] Kagan[5] reviewed the literature on the absorption of dyes, such as trypan blue and lithium carmine, and performed experiments on mice. The general conclusion also appeared to be that absorption of such dyes was conditioned by injury to the mucosa. The most recently published review of the passage of bacteria through the wall of the intestine is that of Arnold.[1] He emphasized the significance of the nature of the diet and the reaction of the intestinal content.

In spite of contradictory results, one is impressed by the frequency with which the significance of injury to the mucosa is stressed by various investigators. Most of the foregoing investigations deal with absorption in the small intestine. Since our interest in the subject was aroused by the clinical problem of obstructing carcinoma of the colon, our experiments were restricted to the colon. Because of the difficulty of satisfactorily demonstrating the presence of bacterial cells in the tissues, we chose to use a fine suspension of graphite commercially known as "hydrokollag 300." If penetration of the mucosa and permeation of the wall of the bowel occur in obstruction, it should be readily possible to demonstrate the presence of these graphite particles locally and in remote organs; whereas the search for bacterial cells in stained sections is notoriously laborious and unsatisfactory. Previous attempts to solve the problem by bacterial cultures have not led to unequivocal results, as we have indicated. Soluble dyes might well have a different mode of absorption than bacterial cells. Insoluble particulate graphite, therefore, seemed to us the most suitable substance to employ for this study.

Method of Study. Nine dogs were used. Under ether anesthesia the colon was obstructed by means of a tape ligature about 15 cm. from the anus, care being taken not to crush the wall of the bowel by tying too tightly. Beginning on the day following operation approximately 50 cc. of the preparation of graphite was given by stomach tube on alternate days. The dogs were allowed their usual diet, but most of them failed to eat, vomited and gradually became emaciated and weak. Several recovered and were in good condition when killed. In these, there was practically no obstruction because of the fact that the ligature had cut through. One died sixteen days following operation apparently because of the obstruction. The other dogs were killed at intervals varying from five days to

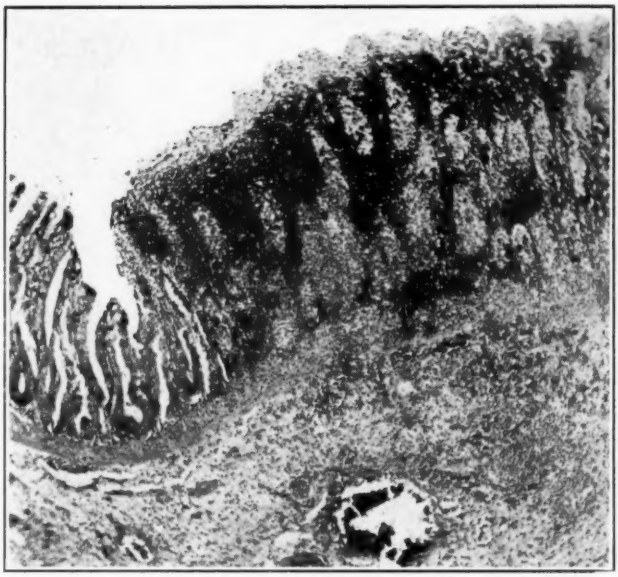

FIG. 1.—Section through a marked hemorrhagic area in the mucosa of the colon of a dog following obstruction (× 75).

FIG. 2.—The distended colon of a dog, twenty-six days following experimental obstruction. Distention involves a portion of the ileum as well. The black areas should appear red. They are due to hemorrhage, not to graphite.

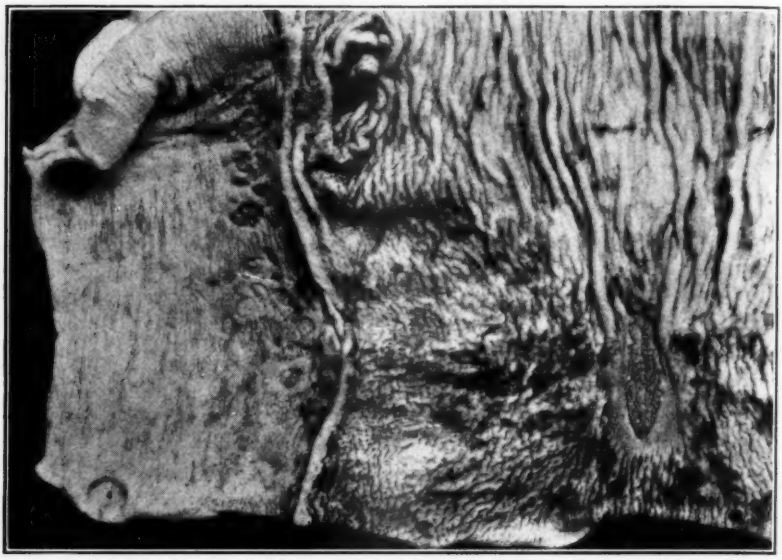

FIG. 3.—The surface of the mucosa of an obstructed colon of a dog, showing ulceration and multiple lesions. Marked pigmentation over the surface is visible. Note ulcerations of the ileal mucosa along the ileocecal valve.

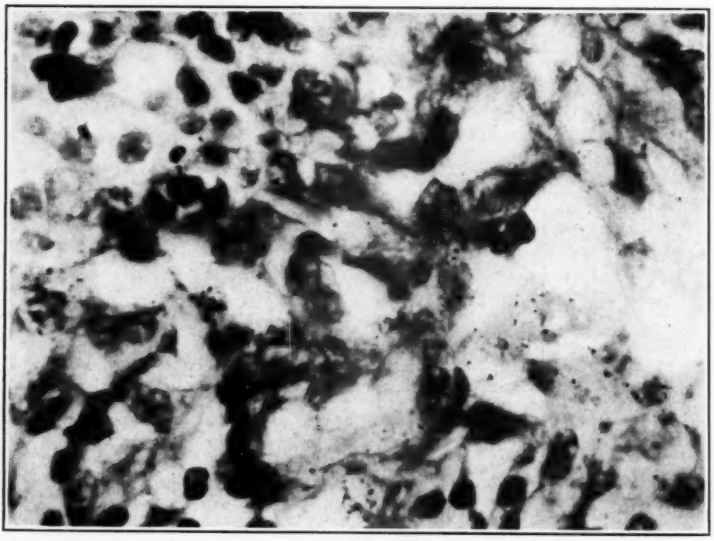

FIG. 4.—Section through the granulation tissue of an ulcer of the colon following experimental obstruction. Particulate graphite is diffusely scattered throughout (× 1100).

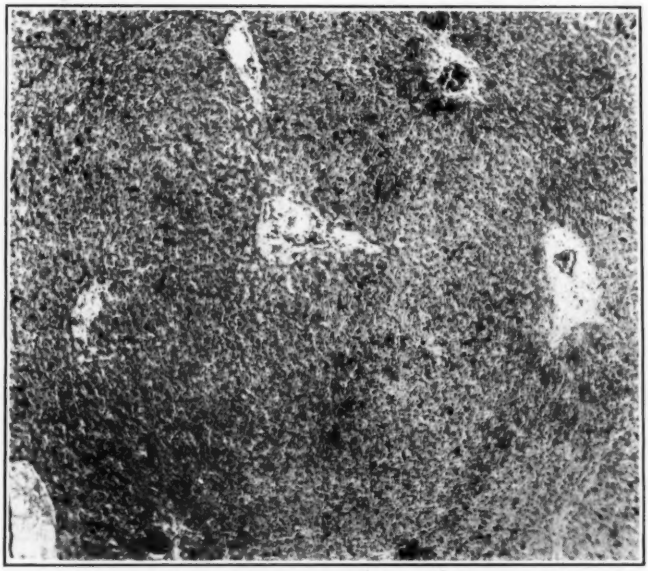

FIG. 5.—Section through the liver of a dog whose colon was obstructed and ulcerated. Low-power view, showing diffuse distribution of graphite (× 75).

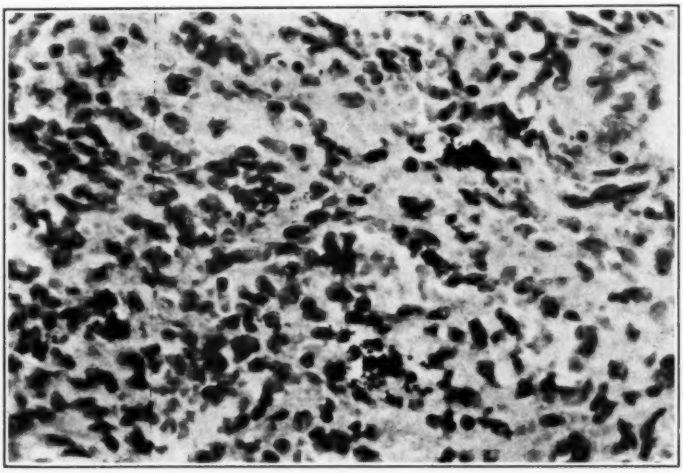

FIG. 6.—Section through the spleen of a dog with obstructed colon with ulceration. Graphite may be observed in blood capillaries and in splenocytes (× 450).

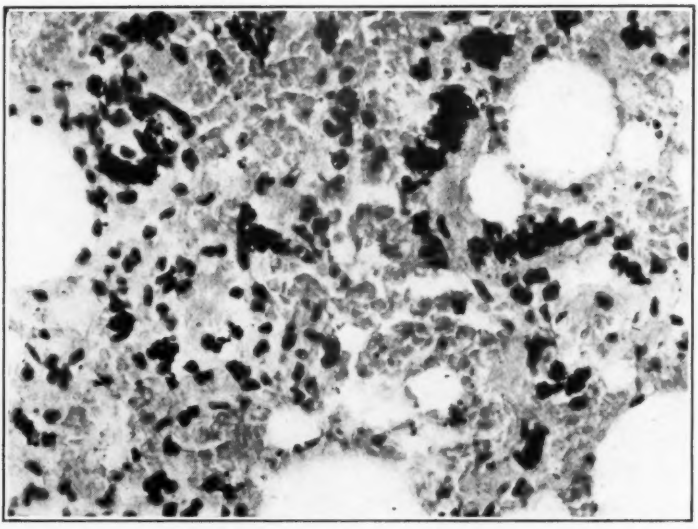

FIG. 7.—Section through the parenchyma of the lung of dog in Fig. 6. Free particulate graphite and large masses in phagocytic cells of the lung may be seen (× 450).

three weeks. The organs were carefully examined for gross evidence of the graphite in the tissues and sections of the colon, small intestine, mesenteric lymph nodes, liver, spleen, lung and heart muscle were taken for microscopic study. These tissues were fixed in formaldehyde and stained with hematoxylin and eosin.

Results. In 6 dogs of our series the search for graphite in the tissues proved entirely negative. One of these was the dog which died. Cause for death, other than obstruction, could not be determined. The colon was markedly distended and was filled with graphite. Ulceration of the mucosa was not found, and particles of carbon did not appear anywhere in any of the tissue. In 2 of the 6 dogs there was practically no obstruction at necropsy two weeks after operation, because the ligature had cut through. Lesions were not found except the healed scar at the site of the ligature, and particles of graphite did not appear in the tissues. In the remaining 3 dogs there was obstruction; in one there was healed shallow ulceration of the colon with lymphocytic infiltration in the submucosa, but in none could the graphite be detected outside of the lumen of the bowel. In 3 dogs there was positive evidence of absorption of the particulate graphite from the obstructed bowel. The necropsy data of these were as follows:

One of the dogs was killed five days after operation because it appeared to be in poor physical condition on account of distemper. Gross evidence of graphite either in the mesenteric lymph nodes or in the subperitoneal regions was not present. The colon proximal to the ligature was distended to about five times the normal size and appeared dark blue, because of the graphite within it. After the colon was opened and washed, the mucosa appeared relatively clear. Several hemorrhagic areas were found on microscopic examination to involve the mucosa and in some regions the muscularis mucosa as well (Fig. 1). Within these hemorrhagic areas were numerous particles of graphite both free and contained in large wandering macrophages. However, particles could not be found in the deeper tissues nor in the intact mucosa. In the liver, on the other hand, scattered black particles appeared in the portal vessels, the sinusoidal spaces, and the central veins. Occasionally such particles could be seen in the Kupffer cells lining the sinusoids. Examination of sections of other organs was negative except for the bronchopneumonic changes of distemper.

The second dog of the series was killed twenty-six days after operation. The animal had continued to lose weight following operation. The entire colon proximal to the ligature was markedly distended. The mucosa of this distended portion as well as two feet of terminal ileum was stained black. This color could be washed from the mucosa with considerable difficulty. Microscopically, it was evident, however, that the staining was due to particles of graphite enmeshed in the surface mucus without penetration of

the mucosa. A shallow irregular mucosal ulcer had developed in the dilated portion of the colon near the point of obstruction; but in this area the particles of graphite were also confined to the mucous deposits on the surface of the mucosa. The stomach contained three superficial ulcers. All the mesenteric lymph nodes were markedly enlarged, but they did not contain particulate graphite. In the liver scattered black particles could be found in the portal vessels and central veins, but they were far from numerous. Examination of all microscopic sections of other organs was negative.

In the third dog, killed twenty-seven days after operation, the entire colon, proximal to the ligature, and the terminal 6 inches of the ileum were tremendously distended, although the obstruction was incomplete (Fig. 2). There were multiple hemorrhagic ulcers in the duodenum, and in the colon there were several shallow irregular ulcerations of the mucosa surrounded by fibrin deposits. A ring of these ulcers was found just proximal to the ileocecal valve (Fig. 3). The under surface of the liver presented a black discoloration suggesting the presence of the graphite, but there were no other gross evidences of absorbed material in any other organ. The mesenteric nodes were not stained, and the thoracic duct, exposed in the chest, was found to be translucent. Microscopically, sections through the ulcerations of the ileocecal area and colon showed granulation tissue with polymorphonuclear and plasma-cell infiltration. Particulate graphite, however, was enmeshed in the surface of the granulation tissue; but none could be identified in the deeper tissues (Fig. 4). Sections of the liver, on the other hand, showed marked evidence of the graphite. Numerous particles appeared, not only in the portal vessels and sinusoidal spaces, but in many of the Kupffer cells which were loaded with the particles (Fig. 5); the same was true in the spleen (Fig. 6). Black particles were abundant in blood spaces, reticulum cells and macrophages. In the lung such particles similarly occurred within pulmonary phagocytes and in the parenchyma as well. These might be difficult to distinguish from the carbon particles of anthracosis; but they did not show a characteristic distribution around the bronchioles (Fig. 7). Results of the examination of sections of lymph nodes, heart muscle and kidneys were negative.

Comment. When this investigation was undertaken it was believed that the tissues of the wall of such an obstructed colon would become thoroughly permeated with the particles of graphite. Such abnormal permeability would offer an explanation for the incidence of peritonitis resulting from handling the bowel and lightly injuring the serosa during operative procedure. Under the conditions of our experiments, however, no such penetration occurred. The only way in which abnormal permeability could be demonstrated in these experiments was not as a diffuse permeation

of the wall of the bowel, but rather as a definite penetration of graphite into the blood vessels of the mucosa and subsequent distribution by the portal blood stream. The only conditions under which such vascular penetration occurs are obstruction, with injury to the mucosa. It appears as if the distending pressure in obstruction actually forces the particles of graphite into the blood stream, but only in the presence of ulceration. Ulceration of the mucosa, without the added factor of marked obstruction, does not lead to this result. There must be obstructive pressure. These observations do not detract from the value of the clinical experience mentioned. It is highly possible, or indeed probable, that in the presence of an obstructing infected ulcer, malignant or otherwise, virulent bacteria actually do penetrate through to the serosa. In the light of our experiments, however; it seems that such penetration must be due to the invasive property of the living bacterial cell, and not to any abnormally increased permeability. Even in obstruction the intact mucosa offers a very effective barrier.

One might speculate on the possible analogy which suggests itself between the results of these experiments and the mechanism of metastasis to the liver. It is an accepted fact that the prognosis in resection for carcinoma of the right side of the colon is better than for a similar condition in the sigmoid, although the growths in the right side are discovered relatively late and are often much larger at the time of operation. The difference is that obstruction occurs earlier on the left side. It is conceivable that in the presence of obstruction and ulceration, cancer cells might be pushed into the portal circulation in a manner similar to our graphite particles. Metastasis to the liver, therefore, would occur relatively earlier and more frequently when the lesion is in the left side of the colon. This mechanism is, of course, only one of many factors to be considered.

Conclusions. The general permeability of the wall of the colon to particulate graphite is not increased in obstruction under the condition of the experiments here reported. In the presence of injury to the mucosa and obstruction, however, particulate graphite may enter directly into the circulation and may be distributed by the portal blood stream.

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INTESTINAL POLYPOSIS WITH AN INSTANCE OF MULTIPLE FIBROMATOUS POLYPS.

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Benign tumors of the intestine may be classified according to their histologic structure. Since the wall of the intestine is composed of different tissues, such as glandular elements, areolar connective tissue, muscle, nerve and bloodvessels, benign tumors may be adenomata, including papillomata, fibromata, myomata, lipomata, angiomata and carcinoids, depending upon the site of origin. Dewis[1] in summarizing 219 collected cases of benign tumors of the intestine, found about 60 per cent to be adenomata, 20 per cent lipomata, 18 per cent myomata and 2 per cent fibromata and hemangiomata.

The term intestinal polyp is used morphologically in a general sense to mean any benign sessile or pedunculated growth that projects into the lumen of the intestine. Any of the above-mentioned tumors that project into the lumen are therefore called polyps. Polyps of the intestine may be either single or multiple. Single polyps may occur at any site along the intestinal tract. Adenomatous polyps are found most often in the large intestine, particularly in the rectum. Nonadenomatous polyps, such as fibromata, myomata, lipomata and carcinoids occur most often in the small intestine, especially near the ileocecal junction.

Multiple polyps may vary in number, from a few, scattered isolated polyps to a diffuse type, numbering many hundreds. The most frequent sites of multiple polyps are the rectum, sigmoid, hepatic and splenic flexures of the colon. Most of the reported cases of multiple polyposis of the intestine were of the adenomatous type. Polyps of the adenomatous type may occur in large numbers

FIG. 1.—Multiple fibromatous polyps in the rectum. (Case I.)

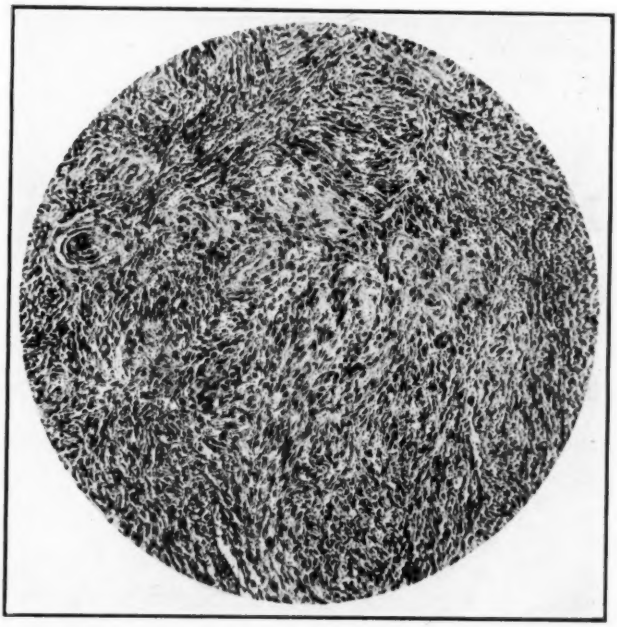

FIG. 2.—Section through a fibromatous polyp of the rectum. (Case I.)

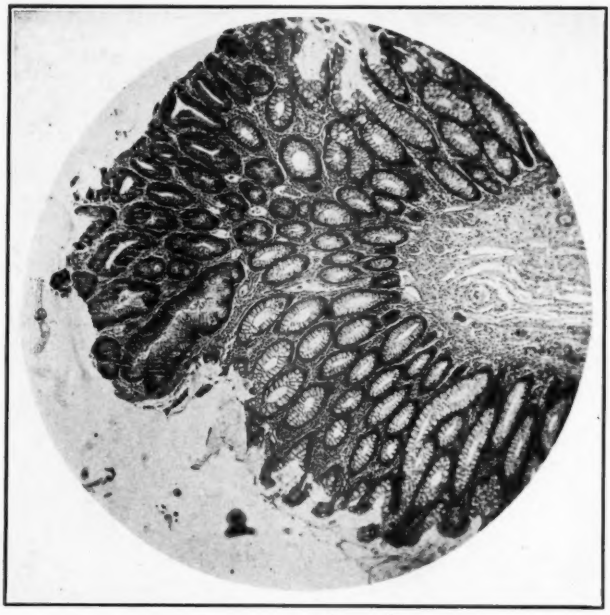

FIG. 3.—Section through a benign adenomatous polyp. (Case II.)

FIG. 4.—Section through an adenomatous polyp undergoing malignant changes. (Case II.)

and in some cases the entire mucosa of the intestine, both small and large, from the pylorus to the anus is studded with countless numbers of tumors, varying in size from a pin-head to a hazel nut. Two cases of nonadenomatous multiple polyposis are recorded in the literature; one, an instance of multiple lipomatosis and one of diffuse myomatosis.

Reviews of the literature on the subject of intestinal polyps are given by Struthers,[2] Doering,[3] Soper,[4] Erdmann and Morris[5] and Saint.[6]

Two instances of multiple polyposis are reported in this communication. The first is a case of multiple fibromatous polyposis associated with chronic ulcerative intestinal tuberculosis. We have not been able to find reports of a similar case in the literature.

Case Report. CASE I.—The patient, a middle-aged Russian salesman, was admitted to Montefiore Hospital complaining of attacks of diarrhea recurring at weekly intervals and a loss of 30 pounds in weight during the past two years. For several months prior to admission he had had incontinence of stool, but had not complained of pain or tenesmus. Nine years prior to admission he had been informed that he had hemorrhoids. At that time a routine Roentgen ray film of his lungs showed a "healed" tuberculous focus in one lung.

The patient was pale and emaciated. Evidence of bilateral pulmonary apical tuberculosis was found. On rectal examination, firm, polypoid masses were felt encroaching on the lumen of the rectum. An intestinal Roentgen ray series suggested the diagnosis of a generalized tuberculous colitis with involvement of the small intestine and cecum.

In view of the severe colonic symptoms with obstructive masses in the rectum, an ileostomy was performed by Dr. Gottesman. Pre-operative and postoperative transfusions were given. The patient ran a septic temperature, had a foul-smelling rectal discharge, became intermittently irrational and died seventeen days after the operation.

Laboratory Data: Marked anemia, red blood cells, 2,450,000; hemoglobin, 40 per cent. The blood Wassermann test was negative. The blood sugar and the blood-urea nitrogen were normal.

A Roentgen ray of the lungs showed tuberculous infiltrations in the left lung from the apex to the seventh rib, with evidence of a cavity, 1½ inches in diameter, in the apical region. Posteriorly, infiltrations were present in the right lung from the ninth to the tenth rib.

Autopsy revealed a chronic pulmonary tuberculosis with cavity formation in the left upper lobe, extensive tuberculous ulcerations of the ileum and cecum, multiple fibromatous polyps of the small and large intestines, chronic passive congestion of the liver, arteriolosclerosis of kidneys, ileostomy, chronic maxillary sinusitis.

Rectum (Fig. 1): On opening the rectum, a large number of prominent sessile polypoid bluish-black masses varying in size from 0.5 to 2.5 cm., were seen projecting above the level of the mucosa. These polypoid masses were quite firm in consistency. The intervening mucosa was grayish and fibrotic and only here and there a small island of normal appearing pink mucous membrane was seen. The cut surface of the polypoid masses was grayish-red, firm and extended to the submucosa. The entire wall of the rectum was markedly indurated and thickened. These masses extended as far up as the sigmoid.

Cecum: Showed several small, blackish polyps, some of which were sessile and some of which were pedunculated. The mucous membrane about some of these polyps was extensively ulcerated.

Ileum: From the ileocecal valve, extending for about 30 cm. the ileum was markedly indurated and thickened. The serosal surface showed numerous, partly caseous tubercles of varying size. The peritoneum was markedly injected in this region. The mucosa presented a striking picture. It was greenish-black in color and some areas were a deep blue. There were many raised, indurated, firm, blue-black polypoid projections from the mucosa. The intervening and surrounding tissue showed extensive, crater-like ulcers sharply defined. The mucous membrane between the ulcers was, in places, strikingly thickened and indurated. The remnants of the ileum and jejunum showed scattered, sharply defined moderately large ulcerations. On the serosal surface beneath these ulcers were numerous tubercles. The mesenteric lymph nodes were large and on section densely fibrotic.

Microscopic Examination. *Ileum:* A large portion of the surface mucosa is completely desquamated and covered with a zone of partly necrotic, partly caseous material. In the submucosa, the muscularis and serosa are scattered large tubercles with central caseation.

A Rectal Polyp (Fig. 2): The mucosa is stripped of its surface epithelium. There is a large nodule which protrudes above the line of the normal mucosa. The interstitial tissue of this nodule shows large areas of hemorrhage and on the surface a wide zone of necrosis. The stroma of the polyp consists of very highly cellular tissue that is arranged in whorls and in irregular strands. The cells are fairly regular and spindle shaped. The submucosa is invaded by this stroma. Van Gieson stain identified this cellular tissue as fibromatous. In many of the nodules and in the intervening connective tissue there is evidence of a simple inflammatory reaction.

Comment. It has long been observed that there is a close correlation between chronic irritation and the development of new growths in the intestinal tract. Rokitansky first called attention to the formation of epithelial hyperplasia in islands of mucous membrane in and about scars and cicatrices of healed intestinal ulcers. The association of other forms of chronic irritation with the appearance of new growths has been thoroughly established. Such irritants may be bacterial, chemical or parasitic.

The coëxistence of tuberculosis and new growths has been observed and the possible etiologic relationship has been suggested. It is well known that in the fibrous scars of lungs in tuberculosis, there is often a hyperplasia of alveolar epithelium. Pathologists have noted the appearance of carcinomata in the walls of bronchiectatic tuberculous cavities.

The tubercle bacillus produces a characteristic tissue reaction. Under certain circumstances it is conceivable that islands of epithelial or connective tissue may be stimulated to overgrowth. It is well known that the stroma of the granulation tissue of Hodgkin's disease, for example, may undergo fibromatous or sarcomatous change. In chronic hyperplastic tuberculosis of the intestine adenomatous polyps are frequently observed, but they are limited to areas of stricture formation. It is possible that in the instance reported in this paper the presence of the tuberculous infection played an etiological rôle in the formation of the new growths.

The following instance is one of multiple adenomatous polyposis complicated by intussusception and malignant degeneration of the polyps.

CASE II.—I. B., female, aged thirty-one years, admitted November 18, 1926, for the past fifteen months has noticed mucous and bloody discharge from the rectum at irregular intervals. There were occasional attacks of pain in the left lower quadrant associated with constipation, nausea and vomiting, with radiation to the groin. For sixteen days prior to admission she had no bowel movement and complained of marked nausea and abdominal distention.

Physical examination revealed an acutely sick female, with marked distention of the abdomen, and tympanites and diffuse tenderness over the whole abdomen. On rectal examination, a large pedunculated boggy mass was felt in the posterior wall of the rectum, just within the internal sphincter. Proctoscopic examination showed an ulcerated tumor on the posterior wall of the rectum, extending upward. The upper limit could not be determined. Biopsy was reported adenocarcinoma.

Laboratory Findings: Hemoglobin, 66 per cent; red blood cells, 3,700,000; white blood cells, 30,000; polymorphonuclears, 89 per cent. Other laboratory data negative.

Diagnosis: The pre-operative diagnosis was intestinal obstruction, secondary to adenocarcinoma of the rectum.

Course: A laparotomy was performed (Dr. Gottesman). The entire gut, both small and large, was markedly distended. In the left lower abdomen was found an intussusception of the descending colon into the sigmoid and rectum. Attempts to reduce the intussusception were unsuccessful and simple cecostomy was done.

The patient's condition improved and on December 4 the abdomen was opened, the outer wall of the intussusception was incised, the intussusception reduced and about 18 inches of the sigmoid was removed. The cut ends of the gut were brought into the abdominal wound. (Operation by Dr. Neuhof.)

Pathologic Report: The specimen consists of two segments of colon:

A. Measures 18 cm. long, 12 cm. wide. The wall is uniformly thickened. The mucous membrane is covered with discrete and confluent soft, fleshy globular and flattened elevations varying from a fraction of a millimeter to several millimeters in diameter. The mucous membrane is everywhere intact except at near what appears to be the upper end, where there is an ulceration of the mucous membrane approximately 3 cm. in diameter. The borders of the ulcer are thin and sloping. The base is covered with a thin layer of mucous membrane or hemorrhagic granulation tissue. Along the cut surface of base of ulcer the muscle layer is distorted and replaced by fatty areolar tissue and dense fibrous tissue. At one place the margin of the ulcer is undermined. The base of the ulcer and the overlapping border at this point is covered with a necrotic yellowish-white tissue. The muscle layer throughout is markedly thickened and edematous. (Its firmness suggests possible malignant infiltration.) The peritoneal layer is edematous, thickened and smooth except for small areas in which there are adherent fibrous tags—broken adhesions.

B. Segment is 15 cm. long, about 10 cm. in circumference, one end of which for a distance of 3 cm. resembles the other specimen. Beyond this line there is a sudden increase in the thickness of the wall which is practically uniform and affects the remaining length of the specimen. At the junction of the thick and thin portions, there is no ulceration, the thicker margin is uniformly smooth, the mucous membrane surface being continuous. There is an area of ulceration approximately 3 cm. in diameter at about the middle of the segment. The ulceration involves the muscle layer. The remainder of the inner surface presents a roughened coarsely granular appearance due to elevations similar to those in the other specimen, and in addition is covered over large areas with an adherent thick yellowish-

white membrane; the underlying muscle is similar to that in the other specimen but in places somewhat thicker. The peritoneal surface is similar to that of segment *A*.

Microscopic examination shows in addition to a marked catarrhal reaction of the mucous membrane, edema of the submucosa and muscle layers and organizing fibrinopurulent exudate on the peritoneal surface. Small areas of mucous membrane are present in which the glands are markedly hypertrophied and irregular, though the basement membrane is intact. These foci of irregular glandular hypertrophy occur on the tips of polypoid-like thickenings of the mucous membrane. In one area the muscle is seen to be invaded by highly irregular glandular structures. A diagnosis of early malignant transformation of multiple polyps with ulceration and chronic colitis was made (Figs. 3 and 4).

Subsequent Course. On June 12, 1927, the cecostomy wound was closed (Dr. Gottesman) and on January 21, 1928, the double-barreled colostomy was closed (Dr. Neuhof). The patient has remained well to date and is entirely symptom free.

Comment. In the preceding instance a long history of chronic ulceratis colitis preceded the appearance of multiple polyposis. It is possible that the long-standing chronic irritation was etiologically related to the formation of the new growths. That intestinal adenomata undergo malignant degeneration is a well-known fact. Various observers estimate that about 40 to 50 per cent of adenomata of the intestine become malignant. Some feel that every case of intestinal carcinoma is preceded by a benign tumor. Mummery traces the various stages in the development of carcinoma from epithelial hyperplasia to adenoma to carcinoma, all following the action of an irritant during a long period of time.

Summary. Two cases of multiple polyposis of the intestine are reported. The first is an instance of multiple fibromata of the small and large intestine associated with chronic tuberculous enteritis. A relation between the chronic irritation and the development of the polyps is suggested. The second instance is one of multiple adenomatous polyps of the intestine complicated by intussusception and malignant degeneration. These two instances again emphasize the etiologic rôle of chronic irritation in the formation of new growths.

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THE INFLUENCE OF MAGNESIUM SULPHATE ON THE SECRETORY ACTIVITY OF THE DIGESTIVE GLANDS.

I. On the Gastric, Intestinal and Pancreatic Secretions.

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In our experiments with magnesium sulphate and the expulsion of bile into the duodenum we were unable to find references to the complete pharmacologic action of this salt on the gastrointestinal tract. The present treatise has to do with the action on the stomach, pancreatic and intestinal secretions, and in a second article we shall summarize our results with the influence of magnesium sulphate on the expulsion and secretion of bile.

1. **Stomach.** In three dogs ("Frant," "Snejok," "Riji"), having Pavlov stomach pouches,* we tried the effect of magnesium sulphate introduced through a gastric tube; and in a fourth dog ("Murzilka") which had both the Pavlov pouch and a gastric fistula we poured the solution directly in through the cannula. The first three dogs had been living in the laboratory for one or more years in good health after the operation, and had been used for other chronic experiments.

Twenty-five to 40 per cent aqueous solution was run in through the stomach tube in "Frant," "Snejok" and "Riji" and allowed to remain. In none of them did we obtain a definite acid secretion. In "Frant" in practically every case there was always within a few minutes nausea and vomiting of a bile-tinged or even a more concentrated biliary secretion mixed with the vomitus. The following is a typical protocol:

TABLE I.—EFFECT OF INTRODUCTION OF MAGNESIUM SULPHATE, "SNEJOK," JUNE 17, 1925.

12:15—Experiment begun.
12:30—One drop from the little stomach (Pavlov pouch).
12:45—One drop.
12:46—50 cc. of 30 per cent magnesium sulphate solution introduced through the stomach tube.
1:00—0.0 cc. from the little stomach.
1:15—0.0 cc.
1:30—0.0 cc.
1:45—0.0 cc.

* For a complete description of the method of making the Pavlov miniature stomach or pouch, see Babkin (Die Äussere Sekretion der Verdauungsdrüsen, Berlin, 1928, p. 180).

In control experiments with water introduced through the tube there was no vomiting and no acid secretion.

TABLE II.—CONTROL EXPERIMENT. "FRANT."

12:15—Brought on the stand.
12:30—0.4 cc. from the little stomach.
12:45—0.3 cc.
12:46—35 cc. of water introduced through the stomach tube.
1:00—0.0 cc.
1:15—0.1 cc.
1:30—0.0 cc.
1:45—0.3 cc.

The results of eleven experiments in "Frant," "Snejok" and "Riji" are given in Table III.

TABLE III.—EFFECT OF MAGNESIUM SULPHATE ON GASTRIC SECRETION FROM THE PAVLOV POUCH. AVERAGE OF ELEVEN EXPERIMENTS.

	Before magnesium sulphate, cc.	After magnesium sulphate, cc.
First fifteen minutes	0.15	0.16
Second fifteen minutes	0.13	0.14
Third fifteen minutes	0.10	0.21
Fourth fifteen minutes	0.12	0.10
Total, one hour	0.50	0.51

In "Murzilka" 25 to 80 cc. of a 25 to 35 per cent solution was put in through the gastric fistula, with the dog on its back, allowed to remain in for five minutes, and then drained out while the dog was placed in the supports; in some cases it was allowed to remain in. The collection was made from the little stomach.

TABLE IV.—"MURZILKA," JULY 8, 1927. LAST FEEDING YESTERDAY EVENING.

15:05—On stand; tube inserted; alkaline reaction; stomach washed with 150 cc. distilled water; returned clear; no nausea.
15:31—Alkaline reaction.
15:31–34—50 cc. of 30 per cent magnesium sulphate solution at room temperature introduced through the gastric fistula; 45 cc. was recovered; no retching, etc.
15:36—Alkaline reaction.

	From large stomach.	From stomach pouch.
15:46	12.0 cc.; strongly alkaline	0.2 cc.; alkaline.
16:01	6.0 cc.; alkaline	0.1 cc.; alkaline.
16:16	4.0 cc.; alkaline	0.6 cc.; neutral.
16:17	20	drops bile-colored fluid
16:18	2.0 cc.; saliva	
16:20	.....	Acid.
16:31	5.0 cc.; strongly alkaline (some bile)	0.3 cc.; acid.
16:46	0.5 cc.; alkaline	0.3 cc.; acid.
For one hour	29.5 cc.	1.5 cc.

The results of ten experiments in "Murzilka" are summarized in Table V. Collection was from the Pavlov pouch.

TABLE V.—INFLUENCE OF MAGNESIUM SULPHATE ON GASTRIC SECRETION.

	Average 6 experiments.	Average 4 experiments.
One hr. before M_gSO_4 . .	0.7 cc.	0.15 cc.
	Magnesium sulphate left in for five minutes	Magnesium sulphate left in altogether.
One hr. after M_gSO_4 . .	1.7 cc.	0.44 cc.
Total average . . .	0.49 cc.	1.18 cc.

2. **The Local Action of Magnesium Sulphate on the Gastric Mucous Membrane.** In two dogs, "Frant" and "Snejok," we washed the little stomach for several minutes with a 15 to 30 per cent solution of magnesium sulphate and determined the rate of flow and the reaction before and afterward. In every one of these experiments except the first the reaction either continued to be alkaline or changed from acid to alkaline.

TABLE VI.—"SNEJOK," JANUARY 6, 1926. THE LOCAL ACTION OF MAGNESIUM SULPHATE (15 PER CENT SOLUTION) ON THE MUCOUS MEMBRANE OF THE STOMACH.

11:40—Dog brought on stand.
13:00—1.2 cc.; acid.
13:15—0.2 cc.; acid.
13:15–20 50 cc. of 15 per cent magnesium sulphate solution run through the Pavlov pouch.
13:20–22—Allowed to drain off.
13:22–28—0.5 cc., neutral.
13:35—0.2 cc, neutral.
13:50—0.3 cc.
14:05—0.0 cc.; mucous membrane is slightly alkaline.
14:20—0.2 cc.; slightly alkaline.

For eighty minutes before the experiments: 1.4 cc.; slightly acid.
For sixty minutes after the magnesium sulphate: 1 cc.; slightly alkaline.

In two other dogs ("Bertha" and "Murzilka"), we introduced the magnesium sulphate directly through the gastric fistula, into the main stomach, allowed it to remain five minutes, drained it off, and then observed the effect on both the large stomach and isolated pouch. The secretion was parallel in the two, that is, the change from acid to alkaline and *vice versa* occurred at about the same time. There was always an alkaline secretion from the stomach. Only once when we used a weak solution of the salt was there an acid reaction. A typical protocol, which also shows the close parallel between the main and isolated stomach, follows:

TABLE VII.—SIMILAR EFFECTS IN STOMACH AND PAVLOV POUCH.

1:30—On stand.
2:15—Tube inserted.
2:15—Alkaline.
2:15–30—0.2 cc.; alkaline.
2:45–53—Alkaline, Pavlov pouch; large stomach neutral; stomach washed with 400 cc. distilled water, 100 cc. at the time, so as not to distend.
2:53—Pavlov pouch alkaline; large stomach neutral.
2:58—Alkaline Pavlov pouch.
2:47–3:02—0.4 cc.; Pavlov pouch, alkaline.
3:17—5 cc.; Pavlov pouch, mucoid.
3:22—Alkaline, both Pavlov pouch and large stomach.
3:23–28—28 gm. of magnesium sulphate in 56 cc. water (33.33 per cent solution in gastric fistula at room temperature; dog on back; recovered 30 cc. clean colorless fluid; no signs of nausea.
3:30—Alkaline in both stomach pouch and large stomach.

	Pavlov pouch.	Large stomach.
3:30–45	0.4 cc.; alkaline	12 cc.; alkaline.
4:00	0.4 cc.; slightly acid	6 cc.; neutral.
4:15	0.3 cc.; slightly acid	2 cc.; very slightly acid.
4:30	0.4 cc.; slightly acid	0 cc.; slightly acid.
4:33–35	....	2 cc.; green-yellow fluid like mixed acid and bile.
	....	
4:30–45		3 cc.; acid.
4:45	0.5 cc.; acid.	

We often also obtained bile in the large stomach, accompanied by retching and vomiting. This will be referred to in a subsequent paper. The presence of the alkaline reaction in the isolated Pavlov pouch shows that it could not have been due to the regurgitation from the duodenum.

Our experiments show that magnesium sulphate acts as a weak irritant to the mucous membrane of the stomach. The effect on the gastric secretion was nearly the same whether the magnesium sulphate was allowed to remain in the stomach or was drained out after five minutes.

3. **Action on the Intestinal Juice.** To determine the effect of magnesium sulphate on the intestinal glands we used three dogs, "Milka," "Achill" and "Zazula," having Thiry-Vela fistulas. In this operation the nerves are intact. "Milka" was operated on one year previously, "Zazula" nine years before and "Achill" two years before. In "Zazula" the loop of gut came from the duodenum and upper jejunum, while in the other two dogs it was from the jejenum. (For complete description of the operation see Babkin: "Die äussere Sekretion der Verdauungsdrüsen," Berlin, 1928.) The magnesium sulphate solution, 25 to 30 per cent was run through in a stream for five minutes, allowed to flow out, and then the fluid collected in an attached graduate, measured every five minutes.

Table VIII shows that the secretion after introduction of the magnesium sulphate is much greater than before. Control solution of physiologic saline run through in the same way as the magnesium sulphate was, without effect.

TABLE VIII.—EFFECT ON INTESTINAL SECRETION. "ZAZULA," APRIL 17, 1925.

11:55—On stand.
12:00—0.1 cc.
12:05—0.1 cc.
12:10—0.0 cc.; 0.2 cc.
12:15–40—0.0 cc.
12:40–45—20 cc. warm 30 per cent magnesium sulphate (38°) and allowed to drain five minutes.
12:55—1.0 cc.
1:00—0.5 cc.
1:05—1.6 cc.; 3.2 cc.
1:10—2.6 cc.
1:20—0.2 cc.; 2.8 cc.
1:25—0.0 cc.
1:30—0.0 cc.
1:35—0.0 cc.; 0.0 cc.
1:45—0.0 cc.
2:00—0.0 cc.; 0.0 cc.

TABLE IX.—SUMMARY OF NINE EXPERIMENTS SHOWING EFFECT OF MAGNESIUM SULPHATE ON INTESTINAL SECRETION.

	Before magnesium sulphate, cc.	After magnesium sulphate, cc.
First fifteen minutes	0.05	1.8
Second fifteen minutes	0.15	1.2
Third fifteen minutes	..	0.5
Fourth fifteen minutes	..	0.3
Totals:		
One-half hour	0.20	
One hour	..	3.9

4. **Action on the Pancreatic Secretion.** We tried the effect on the pancreatic secretion by injecting the magnesium sulphate solution through a tube into the stomach in dogs with permanent pancreatic fistulæ. The results of four experiments are summarized in Table X.

TABLE X.—AVERAGE OF FOUR EXPERIMENTS IN TWO DOGS, SHOWING EFFECT ON PANCREATIC SECRETION.

	Before injection, cc.			After injection, cc.			
	First 15 min.	Second 15 min.		First 15 min.	Second 15 min.	Third 15 min.	Fourth 15 min.
First experiment	0.2	0.2	Magnesium	1.4	1.6		
Second experiment	0.5	0.6	sulphate	2.0	0.5	0.6	1.9
Third experiment	0.5	0.0	(30 per cent)	0.3	0.2	0.6	0.9
Fourth experiment	0.6	0.3	injected in-	0.3	0.7	3.0	0.8
Average	0.4	0.3	to stomach	1.0	0.8	1.4	1.2

These experiments are too few to admit of definite conclusions, nor is it possible to say, without further experimentation, how much of the action is due to the water and to the passage of the tube.

In our protocols the pancreatic juice was somewhat increased

for the first hour after injection. It has been shown in Pavlov's laboratory that water* in the stomach is an independent exciter of the pancreatic juice, that is, it has an action in addition to that of the hydrochloric acid which it also calls forth.

Summary. A 30 per cent magnesium sulphate solution acts in the stomach as a mild irritant, producing a very small flow, which is usually alkaline. In a few experiments with the pancreatic secretion there was a slight increase in the pancreatic juice, which began immediately after giving the magnesium sulphate through the stomach tube. There is, however, a copious secretion of the intestinal glands all along the small gut, produced by the local contact of magnesium sulphate with isolated loops of gut. This occurred in the upper and lower duodenum as well as in the ileum and jejunum.

NOTE.—We desire to thank Prof. V. V. Savitch, of Leningrad, and Dr. Babkin, of Montreal, for suggestions regarding these experiments.

* The other independent exciters of the pancreatic flow are acid, fat and its products, and bile.

THE INFLUENCE OF MAGNESIUM SULPHATE ON THE SECRETORY ACTIVITY OF THE DIGESTIVE GLANDS.

II. ON THE BILIARY SECRETION.

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IN the first paper of this series we showed that magnesium sulphate caused a great flow of intestinal juice, but that it had very little effect on the stomach, and probably but little on the pancreatic secretions.

The results of our experiments in six dogs having various operations on the digestive tract, to be described in the present article, show that magnesium sulphate introduced whether into the stomach or directly into the duodenum has no specific action on the expulsion and secretion of bile.

We previously described the failure to obtain expulsion of bile into the duodenum on the introduction of magnesium sulphate directly into the duodenum through a cannula in a dog having a fistula of the gall bladder.[1]

The next dog, "Sharik," had a choledochus fistula after the method of Pavlov.[2] In this operation the end of the choledochus and surrounding mucous membrane of the duodenum containing the papilla of Vater is brought out on the skin and the duodenum closed. Thus all the secretion of bile has an external flow. We

performed seven experiments altogether in "Sharik" with magnesium sulphate, introducing 25 to 40 cc. of a 30 per cent magnesium sulphate solution through the stomach tube. There was no flow of bile for the first hour in any of these experiments, but in two of them a small amount was expelled during the second hour. In the only case in which we saw a noteworthy expulsion of bile, retching and nausea occurred, a little bile was expelled simultaneously, and a considerable amount the second hour. Control experiments of meat produced a flow; and alkaline mineral water caused an average expulsion of 6.2 cc. for the first hour, and 4 cc. for the second hour, but distilled water was without effect.

Two protocols follow:

TABLE I.—EFFECT OF INTRODUCTION OF MAGNESIUM SULPHATE INTO STOMACH ON EXPULSION OF BILE.

"SHARIK," JULY 24, 1925.

12:45—0.0 cc.
1:00—0.0 cc.
1:15—0.3 cc.; thin yellow.
1:30—0.0 cc.; 0.3 cc.
1:45—0.0 cc.
2:00—0.0 cc.
2:15—0.0 cc.; 0.0 cc.
2:22—25 cc.; 30 per cent magnesium sulphate at room temperature through stomach tube.
2:30—0.0 cc.
2:45—0.2 cc.; at 2:40 retching, and attempt to vomit; bile only after retching.
3:00—0.0 cc.
3:15—0.0 cc.; 0.2 cc.
3:25—Begins to drop.
3:30—0.2 cc.; yellow-brown.
3:45—1.2 cc.; yellow-brown.
4:00—1.0 cc.; yellow-brown.
4:15—1.4 cc.; yellow brown; 3.8 cc.
4:30—2.0 cc.; yellow-brown.
4:45—0.5 cc.; yellow-brown.
5:00—0.2 cc.; yellow-brown.

"SHARIK" AUGUST 8, 1925.

11:10—On stand and duct probed.
11:30—0.0 cc.
11:45—0.0 cc.
12:00—0.0 cc.
12:15—0.0 cc.; 0.0 cc.
12:20–22—43 cc.; 30 per cent magnesium sulphate about 43° C. through stomach tube.
12:30—0.0 cc.
12:45—0.0 cc.
1:00—0.0 cc.
1:15—0.0 cc.; 0.0 cc.
1:30—0.0 cc.
1:45—0.0 cc.
2:00—0.0 cc.
2:15—0.0 cc.; 0.0 cc.
2:16–19—200 gm. fine raw beef, well mixed, 200 gm. distilled water.
3:30—0.0 cc.
2:35—Bile begins.
2:45—1.0 cc.
3:00—1.8 cc.
3:15—2.4 cc.; 3.2 cc.

From this series of uniform experiments it is quite evident that the magnesium sulphate in the stomach caused no effect whatever on the expulsion of bile with the exception of the single instance in which retching and nausea occurred.

In the second dog, "Ajax," the magnesium sulphate was put in directly through a duodenal fistula, the papilla of Vater having been left in its normal position. The operation had been done a month before the experiments, and a cannula inserted into the duodenum. We performed two experiments in this dog, running in magnesium sulphate for five minutes and then allowing it to drain out. In neither experiment did we get a definite spurt of bile, though there was such a spurt after milk was given. There was a marked flow of alkaline duodenal juice, but it contained very little bile.

TABLE II.—EFFECT OF INTRODUCTION OF MAGNESIUM SULPHATE INTO DUODENUM. "AJAX," OCTOBER, 7, 1925.

10:15—9 cc.; golden-yellow bile, coming in spurts, sometimes cloudy.
10:25—18 cc.; 27 cc.
10:30—6 cc.; light amber.
10:35—3 cc.; light amber.
10:40—5 cc.; 14 cc.
10:45—3 cc.; light straw.
10:50—0 cc.
10:55—1 cc.; yellow; 4 cc.
11:00—0 cc.
11:05—0 cc.
11:10—0 cc.; 0 cc.
11:10—25 cc.; 30 per cent magnesium sulphate run in for five minutes through fistula, allowed to run out; 13 cc. yellow bile-colored fluid obtained.
11:20—11 cc.; yellow (duodenal juice).
11:25—3 cc.; straw color.
11:30—11 cc. dirty straw; 25 cc.
11:35—4 cc.; straw.
11:40—6 cc.
11:45—3 cc.; 13 cc.
11:50—0 cc.
11:55—0 cc.
12:00—0 cc.; 0 cc.
12:05—25 cc. milk given just as magnesium sulphate (allowed to remain five minutes, and then run out 10 cc. returned).
12:10—
12:11—Bile appears; 5 cc. milk.
12:15—3 cc. acid.
12:19—3 spurts of pure bile.
12:20—1 cc.
12:25—4 cc.; 8 cc.

The third dog, "Spot," had a stomach fistula and also the choledochus fistula after Pavlov as in "Sharik." The dog was turned on its back and 25 to 40 cc. of magnesium sulphate at room temperature run into the stomach, and allowed to remain there. In two experiments, after a latent period of three minutes a definite flow of darker bile set in. In the other two experiments, there was no expul-

sion of bile whatever for an hour after the injection. This expulsion of bile may have been due to the coincidence with the periodic secretion or something in the procedure.

In two other dogs, "Murzilka" and "Frant," we introduced magnesium sulphate through the stomach tube. "Frant" vomited every time and in each instance the vomitus was bile colored. "Murzilka" had a gastric fistula, and we could observe the contents of the stomach. It seems significant that in five of the six experiments there was no regurgitation of bile and no retching or nausea, and that in the single case in which more than a trace of bile was present there was retching.

Effect on the Secretion of Bile. In one dog, "Tulpan," which had a gall bladder fistula with the choledochus tied so that all the secretion could be collected and measured, we introduced 50 to 70 cc. of 30 per cent magnesium sulphate solution through the stomach tube, and allowed it to remain. The quantities before and after introduction are shown in the following table.

Control experiments of distilled water and of alkaline mineral water had little or no effect on the amount of bile secreted. (Experiments of Drs. Gefter and Martinson.)

TABLE III.—CONTROL EXPERIMENTS (DISTILLED WATER AND ALKALINE MINERAL WATER.) AVERAGE OF SIX EXPERIMENTS.

	Bile excreted.
Two hours before injection	7.5 cc.
One hour before injection	4.2 "
Two hours after injection of magnesium sulphate in stomach	9.5 "
One hour after injection of magnesium sulphate in stomach	6.6 "

Although this seems to indicate a slight effect on the amount of bile secreted, the material we have is not enough to be conclusive.

We feel we can state with assurance, however, that in the dog, 30 to 40 per cent magnesium sulphate solution introduced either directly into the stomach or the duodenum has no effect on the expulsion from the gall bladder. In the few cases when bile appeared it could be explained by the nausea and retching. Frazer[7] found after injecting magnesium sulphate into the duodenum no increased secretion of bile from a choledochus fistula, though he employed a slightly different operative technique from ours.

Summary. My own clinical experience, as well as that of Lyons, Friedenwald and other prominent gastroenterologists, showed that there was very often a flow of bile from both the biliary passages and gall bladder after magnesium sulphate introduced through a stomach tube. Subsequent experimental work on dogs in which the magnesium sulphate was put directly into the duodenum rarely produced bile and never any increase of pressure in the gall bladder. In other dogs in which we gave the magnesium sulphate by mouth

through a tube, bile was usually secreted; but some of these animals never reacted in this way. Finally in another dog in which we ran the magnesium sulphate directly into the stomach through a fistula we sometimes got bile regurgitated and sometimes did not.

Reviewing our results, we found that the dog in which we always obtained bile was one which always had nausea and vomiting after the magnesium sulphate, those which never gave bile never had nausea and vomiting after the procedure; and in the one in which we sometimes found bile and sometimes did not, whenever there was bile it was preceded by nausea and vomiting and when there was no nausea and vomiting there was no bile.

This reconciled our own clinical and laboratory results in man and in dogs, and, furthermore, we think clears up much of the mystery of magnesium sulphate which has lasted for a decade. It is quite likely that magnesium sulphate may cause a contraction of the duodenum (Auster and Chron, Diamond, Kawashima), and a local relaxation of the sphincter of Oddi, and under these conditions if there is nausea or vomiting, which may quite readily be produced by the passage of the tube alone or by the injection of substances into the duodenum, or under other conditions bringing about expulsion from the gall bladder as shown by Winkelstein, there may follow expulsion of bile from the bladder into the duodenum. We must remember that a large number of other substances in the duodenum also produce a flow of bile, and that bile enters the duodenum periodically.

Recently an assistant of Pavlov, K. M. Bykov,[10] has shown that conditioned reflexes may play a part in the secretion of bile, and moreover that this secretion may be an enteroreceptory one (that is, from the internal nerves) instead of an exteroreceptory one (as for example from the eye, ear, skin).

If this is so—that even so complicated a process as the secretion of bile may be conditioned, then it is quite clear that if there were (as there usually is in most patients) nausea and vomiting from the introduction of the duodenal tube and the magnesium sulphate, once or several times, with the expulsion of bile, the flow might subsequently become conditioned to the method of the procedure even though the nausea failed to appear. The nausea and antiperistalsis could thus explain the expulsion of bile occurring the first times, and it seems quite likely in view of Bykov's experiments, that later, in those patients who are drained often, there might be a conditioned flow elaborated which is analogous to that of Pavlov's conditioned reflex.*

* Bile (unconditioned stimulus) was injected into the blood and there followed an increase of the bile secretion (unconditioned reaction). This procedure was repeated a good many times. Later on, merely putting the dog on the stand and making the necessary preparations for the injections (conditioned stimulus) proved sufficient to increase the biliary secretion (conditioned reaction).

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A NEW NEEDLE GUARD AND GUIDE FOR PARAVERTEBRAL NEURONE BLOCK INJECTIONS.

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In certain conditions of great pain, such as in severe angina pectoris, herpes zoster, meralgia paresthetica, tabetic crisis and so forth, it is sometimes necessary to infiltrate the spinal nerve roots in the thoracic region with different medicines. This procedure

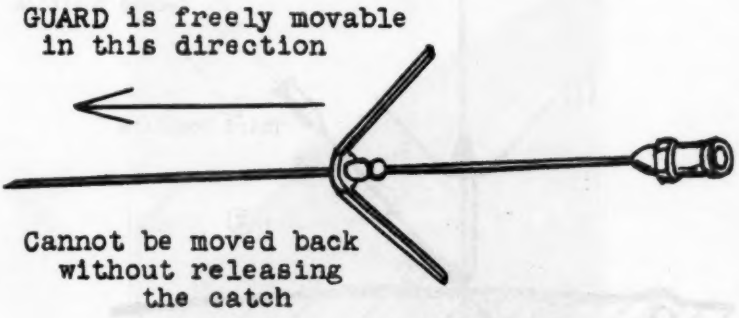

Fig. 1.—Needle guard and guide for paravertebral neurone block injections.

has also been used for the immediate relief of severe pain associated with cancerous growths in the thoracic cavity and its walls, as well as in paravertebral spinal anesthesia.

The proper insertion of a hypodermic or long spinal needle into

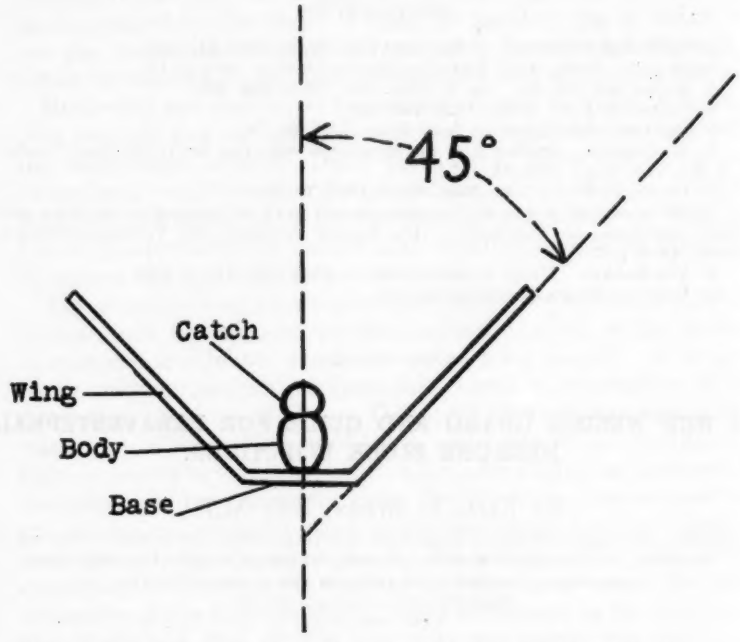

FIG. 2.—Needle guard and guide for paravertebral neurone block injections.

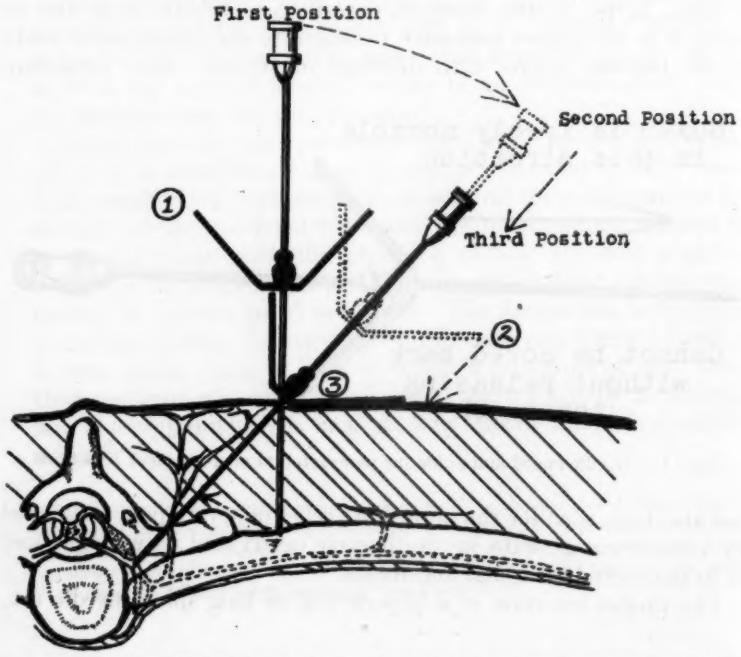

FIG. 3.—Diagram of spinal nerve, showing how the instrument localizes the posterior root.

the desired area is one of extreme difficulty, not only because of the bony impediments offered by the spinal column and the thoracic

FIG. 4.—Patient lying on side. Needle in first position; diagrammatically shown in Fig. 3.

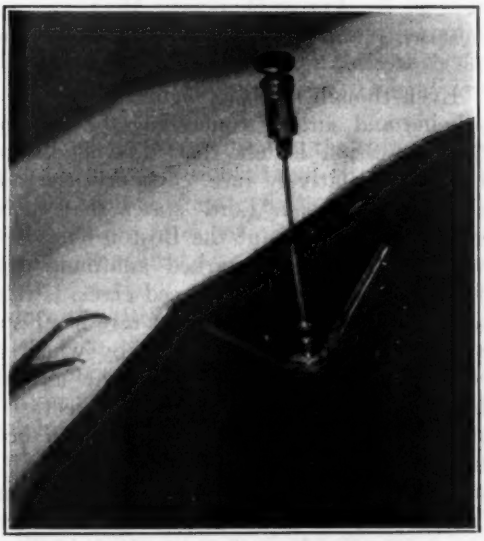

FIG. 5.—Needle in third position; diagrammatically shown in Fig. 3.

framework, but also because of the ever-present danger accompanying injury of vital structures.

The device here offered to overcome any difficulty and danger consists of an adjustable guard placed on the needle, and held there in such a manner that it can easily be moved away from the hub, but not toward it (Fig. 1). This is accomplished by a special catch which holds the guard on the shaft of the needle. The wing of the guard (Fig. 2) has an inclination of 45 degrees with the base of the guard.

To use the guard for paravertebral work, insert the needle perpendicularly to the surface of the back, about 4 cm. from the spinous processes, until you hit the lower margin of the rib above the nerve root to be injected. Then adjust the guard (Fig. 3, 1) to a distance of 2 cm. from the surface of the skin, which distance is also equal to the *length* of the wing. Then slightly withdraw the needle, and tilt it sufficiently to make the wing parallel to the surface of the body (Fig. 3, 2). This will bring the needle to an inclination of 45 degrees. Now push the needle in, at this inclination, until the guard hits the skin, thus preventing it from going any further (Fig. 3, 3). The needle will then be in position for the injection.

BRONCHIECTASIS.

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Incidence. Even though no exact figures are given in the textbooks on medicine and surgery concerning the incidence of bronchiectasis, the impression is left that this condition of chronic pulmonary disease is relatively rare, certainly much less frequent than pulmonary tuberculosis. Lord[1] states that there were only 38 cases among 3183 autopsies at the Boston City Hospital. Undoubtedly bronchiectasis, with marked anatomic change in the bronchi, as found at autopsy in advanced cases, is relatively rare. That bronchial dilatation, however, is not rare has been repeatedly shown since the introduction of methods by which the tracheobronchial tree may be visualized. From the author's personal experience, he is forced to conclude that bronchiectasis is the most frequently encountered chronic pulmonary affection, occurring even more frequently than pulmonary tuberculosis. That many cases of bronchiectasis, nontuberculous in nature, are being diagnosed and treated as tuberculosis at the present time has been definitely shown. That such errors have been made is easily understood. A patient with a persistent cough lasting over a period of years, which resists all forms of therapy, has in the past been considered tuberculous, even though the sputum has been repeatedly negative.

Such an individual has been given the "benefit of the doubt," and has been referred to a tuberculosis sanitarium. From 25 to 50 per cent of all inmates of tuberculosis sanitaria are nontuberculous (Hamilton[2]). That bronchiectasis may be caused by tuberculosis must not be forgotten, but this type of bronchiectasis is relatively rare as compared with the nontuberculous type.

Etiology.—The etiology of bronchiectasis is varied. Many conditions have been blamed for the pathologic changes occurring in the bronchi. A fetal bronchiectasis was first described by Grawitz,[3] who contended that bronchiectasis was the result of congenital cystic changes in the lung. Sauerbruch[4] is a recent champion of the congenital theory. Duken[5] believes that a few cases of bronchiectasis are congenital. He considers that the predisposition to bronchiectasis is congenital, as bronchiectasis is often associated with other congenital abnormalities, such as idiocy and imbecility. Henschen[6] and Willy Meyer[7] consider a congenital malformation as a possible cause of bronchiectasis.

Cirrhosis of the lung was considered the cause of bronchiectasis first by Corrigan.[8] Since this time Henschen,[6] Meyer,[7] Kaufmann,[9] Schott,[10] Steinmeyer and Kathe,[11] Duken,[5] and Findlay and Graham[12] believe that cirrhosis of the lung may play an etiologic rôle. Chronic pneumonia has been mentioned as a cause of bronchiectasis by Henschen,[6] Findlay,[13] and Adams.[14] Hedblom,[15] Meyer[7] and Waetjen[16] believe that in bronchiectasis there is an alteration in the bronchial gland mucous secretion which, normally, is bactericidal. The secretion, having lost its bactericidal property, permits the growth of organisms. As a result of this infection there is weakening of the bronchial wall, allowing dilatation to occur. Duken[17] is of the same opinion.

That acute infectious diseases may be the cause of bronchiectasis has been shown by Duken,[5] Elliott[18] and Graham.[12] Opie and his coworkers[19] and Mikulowski[20] state that of the various acute infections influenza, pertussis and measles occur most frequently as causative agents in bronchiectasis. Of these, influenza undoubtedly occupies first place, as the incidence of bronchiectasis has increased considerably since the 1918–1919 pandemic of influenza.

Attention has been called to the fact that chronic sinusitis is usually associated and may be the cause of bronchiectasis in a large percentage of cases. Rist,[21] in 1916, first demonstrated the association between chronic coughs and sinusitis. More recently the etiologic rôle which sinusitis plays in bronchiectasis has been stressed by Mullin,[22] Webb[23] and Adams.[24] Sinusitis is such an important cause of bronchiectasis that the possibility of a bronchiectasis developing in every persistent case of sinusitis must be considered.

The loss of nerve control of the bronchi is considered by Lebert[25] and Biermer[26] to be a cause of bronchiectasis. Stenosis of the bronchi, producing obstruction to the outflow of air, is considered

as a cause of bronchiectasis by Schott,[10] Franke,[27] Sauerbruch[4] and Kaufmann.[9] The obstruction may be the result of a congenital narrowing, an inspired foreign body, or a neoplasm. In all cases of bronchial stenosis a bronchial dilatation occurs distal to the obstruction, but obstruction is probably a *relatively* infrequent cause of bronchiectasis.

Of all the various causes of bronchiectasis, the one most frequently responsible for the condition and, therefore, the one most important is a chronic inflammatory process involving the bronchi, that is, chronic bronchitis (Andral,[28] Stokes,[29] Findlay and Graham,[12] Sauerbruch,[4] Kaufmann[9] and Duken[5]). In the author's experience bronchitis is by far the most frequent cause of bronchiectasis. In a series of young University students suffering from chronic bronchitis or attacks of acute bronchitis, giving no clinical evidence of bronchiectasis, a definite bronchial dilatation was found in over 90 per cent.[30] Brauer[31] considers early stages of bronchiectasis as arrested catarrhs in the lower lobes of the lung.

Pathologic Anatomy.—In postmortem and lobectomy specimens certain characteristic pathologic findings can be demonstrated in bronchiectasis. As the name implies, the bronchi are dilated. There are three main types of dilatation: (1) the cylindrical; (2) fusiform; (3) saccular. Sauerbruch[4] believes that it is possible to differentiate between the first and last of these types etiologically, as he considers the sacculated variety a congenital anomaly, whereas the cylindrical variety is usually the result of inflammatory change. Dilatation may occur in the bronchi, bronchioles or both. The mucosa lining the bronchi may either be hypertrophic or atrophic. In the early stages, there is usually hypertrophy, whereas later atrophy occurs. In the hypertrophic areas papillomatous growths may occur, which are exceedingly vascular. Sauerbruch[4] states that the inflammatory process begins first as a catarrhal swelling in the mucous membrane with a marked cellular infiltration. The smoothness of the bronchial mucosa disappears. There is often hypertrophy of the entire wall of the bronchus. The mucous glands, the cartilage and the peribronchial structures are enlarged. There is calcification of the degenerated portions, especially in the region of the cartilage. Because of the mucosal involvement there is a diffuse purulent secretion. The epithelium may be intact or may be desquamated, resulting in ulceration from which hemorrhage is apt to occur. In the advanced stages of the atrophic form, the bronchial musculature and elastic fibers, as well as the mucous glands, and even cartilage, are destroyed, the entire wall being replaced by fibrous tissue. In these advanced forms, the pulmonary tissue surrounding the bronchi shows definite changes, such as fibrosis and atelectasis. These pathologic findings in the lung and the bronchi, which are well known to all pathologists, represent, however, the late stages of the condition, bronchiectasis. The

author is of the opinion that by far the greater number of cases of bronchial dilatation seen, and clinically improved by the introduction of iodized oil into the tracheobronchial tree, have relatively little anatomic change in the bronchial wall. In four personally observed cases in which, both clinically and radiographically, bronchiectasis was definitely diagnosed, not only the clinical symptoms were relieved following the introduction of adequate therapy, but also the radiographic evidence of bronchiectasis disappeared. In these patients, bronchiectasis, in an anatomic sense at least, did not exist. In all probability a functional dilatation of the bronchi precedes any anatomic change. This dilatation probably is caused by atony of the bronchial musculature, which has been acted upon by bacterial toxins, aided by stagnation of retained secretions. No definite period is required for anatomic changes to occur, which may appear either after short or long intervals. The lower lobes are by far the most frequently involved, the left more frequently than the right. According to Sauerbruch,[4] the left lower lobe is involved in from 80 to 95 per cent of all cases. The condition may be found, but is relatively rare in the upper lobe; in fact, it is questionable whether a nontuberculous bronchiectasis ever occurs in an upper lobe without there also being an involvement of the lower lobes. The reason the lower lobes are most frequently involved is probably because of the stasis of the retained secretion. The reason the lower left lobe is more frequently involved than the right is not known. Sauerbruch[4] believes that as a result of a congenital malformation there is more apt to be obstruction in the left bronchus than in the right. Duken[5] is of the opinion that the left lower lobe is involved more frequently than the right, because the left bronchus comes off the trachea at a more acute angle than the right and because the pulmonary artery crossing on the left produces a slight constriction of the left main bronchus just before the upper bronchus is given off. The lesions are bilateral in over half of the cases.

Symptoms and Signs.—The clinical picture, as described in most of the textbooks on medicine and surgery undoubtedly represents a late stage of the condition. If one waits until the patient presents a picture of marked pulmonary suppuration, considerable time will be lost. While undoubtedly there are many cases of such advanced stages of bronchiectasis, these are much less frequently encountered than the early, less advanced cases. The clinical picture often described is as follows: A patient who has had an antecedent pulmonary infection expectorates large amounts of fetid suptum, varying from a few cubic centimeters to 1000 or more cubic centimeters in twenty-four hours. The expectoration is often described as being "mouthful" in type, that is, the patient, following a paroxysm of cough, will bring up a mouthful of sputum. This is associated with fever, anorexia, and loss of weight. There are, however, late symptoms. The early symptoms and signs of bronchiectasis, and those

which occur at the time a diagnosis should be made so that the proper therapy might be instituted, are relatively insignificant. The author found in a group of apparently normal young university students, who complained of persistent cough or recurrent attacks of cough, either associated with or without sputum, and in whom a diagnosis of chronic bronchitis had been made, a definite bronchial dilatation in 92 per cent of the cases. The diagnosis in each case was made bronchographically. Some of these patients had no sputum, representing the "dry bronchiectasis" of Bezançon;[32] others had a cough associated with a slight amount of sputum, usually present only when the patient suffered from an acute respiratory infection. The sputum in this type of case is rarely fetid, although at times it may have a slightly unpleasant odor and taste. Except in the case of "dry bronchiectasis," the effect of posture on the cough and sputum has been almost invariably noted. Patients often find that by assuming certain positions, especially at night, the cough and expectoration are apt to be aggravated. This depends upon the mechanical drainage of the bronchioles allowing the retained secretion to enter the more sensitive portions of the bronchi, which induces coughing. Early in bronchiectasis the cilia of the bronchial mucosa are lost, permitting a stagnation of the secretion in the terminal bronchi and bronchioles.

Hemoptysis is a frequently encountered symptom, being present in from 50 to 70 per cent of cases. Seldom is bleeding severe; very frequently, however, a tinging of the sputum with blood is noted. Clubbing of the fingers is present only in the advanced cases and those in which the condition has existed for a long period of time. Except in advanced cases, the patient feels well, aside from some slight lassitude. They often complain of not having the amount of energy which they usually have, although they are able to perform their work comparatively well. Because of rather vague, indefinite symptoms, these individuals are often branded as neurotics. Such a patient has been described in detail in a previous publication by the author.[33] In 25 cases reported by Findlay[13] cough was present in 24 and absent in 1. Expectoration was present in 17 and absent in 6. In 50 per cent of Elliott's[18] cases a previous diagnosis of bronchitis had been made. In all probability bronchiectasis was present at the time the diagnosis of bronchitis was made. Fever and chills are relatively rare in bronchiectasis and in the early cases are practically never encountered. That bronchiectasis may occur with relatively few signs and symptoms was shown by Duken.[5] "We have discovered bronchial dilatation by means of the filling procedure (bronchography) in cases in which clinical findings showed nothing more than a slight bronchitis and in which the history completely failed."

The physical findings in bronchiectasis also vary. In by far the majority of cases and in all of the early cases the physical findings

are minimal. Almost invariably, however, there is some lagging on the affected side, especially at the base. Characteristically, there is no change in the percussion note except in the late cases. Diaphragmatic excursion is usually normal. Auscultation reveals relatively little, although moist râles, which persist after coughing, are usually audible at the base of the lung. These are not infrequently localized in a relatively small area, and special care must be taken in order to detect them. In the advanced cases marked limitation of motion is present; there is impairment of resonance over the affected lobe, due to an associated pneumonitis; moist, bubbling râles are audible; bronchial breathing is present. In advanced and long-standing cases of bronchiectasis there is flattening of the affected side of the chest, due to the pulmonary cirrhosis, and there may be some curvature of the spine. Pulmonary osteoarthropathy is present in most of the cases in which the condition has existed for a long period of time.

Diagnosis.—Before the use of iodized oil as a contrast substance, the diagnosis of bronchiectasis was made on the history, physical findings, and, occasionally, by means of the Roentgen ray plate. It was then not difficult to diagnose the advanced cases with their typical history and physical findings. The Roentgen ray was of value in those cases in which bronchiectasis was marked and when the process was limited to the right side. As in the majority of cases of bronchiectasis the pathologic process is limited to the left side, it is evident that a roentgenogram was of limited value, because the cardiac shadow obscures the lung parenchyma and bronchi.

With the introduction of lipiodol by Sicard and Forestier,[34] in 1922, as a contrast substance, it became possible to visualize a tracheobronchial tree by means of the Roentgen ray and thus demonstrate any deviation from the normal outline of this system. The procedure became quite popular and was valuable in confirming the clinical diagnosis of bronchiectasis in those patients presenting typical clinical signs and symptoms of the condition. At the present time it is generally accepted that a diagnosis of bronchiectasis should not be made unless positive roentgenographic evidence is obtained following the introduction of a contrast substance in the tracheobronchial tree. The greatest value of bronchography is, however, not sufficiently appreciated at the present time. Even before the introduction of iodized oil, it was not difficult to diagnose the advanced case of bronchiectasis. These cases can be correctly diagnosed at the present time without the use of bronchography, even though the extent and exact location of the process may be difficult to determine without it.

Bronchography is of special value, however, in the early, relatively mild cases in which the symptoms are minimal, such as those cases of bronchiectasis in which cough, with or without expectoration is the only symptom. The diagnosis which is usually made in these

cases is chronic bronchitis or recurrent acute bronchitis. If much is to be accomplished in the treatment of bronchiectasis, it is necessary that the diagnosis be made early. In the group of university students referred to above, there were neither symptoms nor signs suggestive of the true pathologic lesion. The only symptom present in most of these cases was cough. In all a diagnosis of chronic bronchitis had been made. Two of these cases have been described in detail in a previous publication.[33] In performing a bronchography it is essential, in order to avoid an error in diagnosis, that the fluoroscopic observation of the mode of filling of the bronchi be made. This is one of the most important factors in making a correct diagnosis, because of the possibility that the iodized oil may pass into the alveoli and produce such a haziness that the bronchi may be obscured. The author has observed 6 cases in which a diagnosis of bronchiectasis was very definite during the first few minutes following the introduction of the contrast substance into the tracheobronchial tree. A roentgenogram of the chest, made about sixty seconds later, showed the outlines of the bronchi so obscured by oil in the alveoli that it was impossible to detect any bronchial dilatation. The importance of the fluoroscopic observation of the mode of filling of the bronchi, in order to prevent a false impression being obtained as a result of two bronchi being superimposed upon one another, has been emphasized by Lenk and Haslinger.[35]

Treatment.—The treatment of bronchiectasis in the past has been both medical or conservative and surgical or radical. Because, however, the medical treatment has been more or less unsatisfactory and yielded relatively few results, surgery in bronchiectasis has been much more frequently employed. To quote Whittemore,[36] "Medical treatment may be dismissed by saying that it cannot cure any case, although, if the patient can devote his life to taking care of his health, spending his winters in a dry, warm climate, using postural drainage, it may be that he will live a long and fairly comfortable life. There is no drug that has any definite influence in curing the disease." On the other hand, Sauerbruch[4] states, "The surgical treatment of bronchiectasis is certainly the hardest and least thankful chapter of the entire lung surgery."

The surgical treatment of bronchiectasis dates back to 1873, when Mosler[37] suggested that bronchiectatic cavities be opened and drained. Bronchotomy, however, because of the almost uniformly bad results obtained, has been almost entirely abandoned. Mumford and Robinson,[38] in 1902, collected 33 cases of bronchiectasis from the literature in which a bronchotomy had been performed, with a mortality of 62 per cent. Garre[39] had a 37 per cent and Koerte[40] a 78.6 per cent immediate mortality, following surgical drainage in bronchiectasis. In 1911, Sauerbruch[4] was able to collect 123 cases of bronchiectasis which had been treated by pneumonotomy.

Thirty-three per cent were cured, 5 per cent were improved, 27 per cent were unimproved and 35 per cent died. Within recent years, however, beneficial effects in isolated cases have been reported by Lilienthal,[41] Ribadeau-Dumas and Mocquot.[42] The pneumonotomy performed by Graham in his cautery pneumectomy will be discussed under lobectomy.

Sauerbruch,[4] because of the high mortality obtained following pneumonotomy in bronchiectasis advocated the production of fibrosis of the lung by ligating the pulmonary artery. In 1911, he reported 2 cases of bronchiectasis so treated. Henschen[6] reported the result of 7 cases operated in Sauerbruch's Clinic in this way. One patient showed extensive improvement, practically a cure. In another there was slight improvement. In 2 no change was demonstrated. In 2 others, no conclusions could be drawn, because the report was made too soon after operation. In the last case it was necessary to resort to pneumonotomy. Because of the marked shrinkage and fibrosis of the lung produced by this procedure, Henschen[6] advised that the ligation of the pulmonary artery be followed by a thoracoplasty.

At the present time the most widely practised surgical procedure in bronchiectasis is some form of surgical collapse. Mumford and Robinson,[38] in 1912, advocated the production of an artificial pneumothorax in those cases of bronchiectasis in which there were no adhesions between the parietal and visceral layers of pleura. McGregor[43] believes that an artificial pneumothorax should be used in all cases of bronchiectasis as a preliminary procedure. Artificial pneumothorax has been used recently by Duken,[5] Brauer[31] and Whittemore.[44] In a review of the literature by Whittemore and Balboni,[44] 93 cases of bronchiectasis were collected which had been treated with artificial pneumothorax. Fourteen were reported as cured; 44 reported as improved, this improvement varying from slight to really great improvement; 7 died, 2 of which deaths followed thoracoplasty; in 12 cases a pneumothorax could not be produced; and there was a rupture of the pleural cavity in 3. Whittemore and Balboni conclude, however, that, even though a review of the literature shows such a high percentage of cures following the production of an artificial pneumothorax, this procedure should not be considered a curative measure. They feel, however, that it may be used as a preliminary procedure, and if no lasting benefit is obtained following its use more radical surgery can always be resorted to.

The form of collapse therapy which is most frequently employed at the present time is that of thoracoplasty. Koerte,[40] in 1908, reported 3 cases of bronchiectasis in which a thoracoplasty had been performed. One of these died of brain abscess; in one the results were uncertain; and in one a cure resulted. Mumford and Robinson[38] in 1912, reported 3 cases in which an extensive rib resection had been

performed with two deaths and one patient barely escaping death. Sauerbruch,[4] in 1911, reported unfavorable results following the production of a thoracoplasty in bronchiectasis. He emphasized at this time the necessity of energetic orthopedic after treatment in cases in which a thoracoplastic operation has been carried out. In 1920, he reported his results in 27 cases; 5 patients were permanently benefited, one obtained only temporary improvement, one died and one became worse after a year. In 11 cases there was definite improvement. Henschen[6] reported 14 cases treated by thoracoplasty in Sauerbruch's Clinic. Two patients were improved to such a degree that they might be considered cured; 4 were somewhat improved, and the remaining 14 showed practically no results. There was no mortality. Hansen[45] reported 2 cases in which thoracoplasties were performed with absolutely no results. Hedblom[15, 46] has been the American exponent of the extrapleural collapse in bronchiectasis, and has especially emphasized the value of "graded" thoracoplasty. In 1924, he reported 18 cases in which an extrapleural thoracoplasty had been performed for bronchiectasis. There was no postoperative mortality, and at the time of report there were no deaths. Following this procedure the decrease in sputum averaged from 75 to 100 per cent. In 1927, a subsequent report was made on this series of cases, all patients having been followed for three years postoperatively. Three had died, one of fatal hemoptysis, one of actinomycosis of the chest wall ten minutes after operation and the other of acute poisoning. Six had been markedly improved, the sputum ranging from an average of 60 to 90 cc. in twenty-four hours. Five had been practically cured. One of these 5 still raised from 60 to 90 cc. of sputum, whereas before operation he raised from 500 to 1000 cc. In the same year, Hedblom[46] reported the records of 9 additional patients, 2 of whom died of pneumonia following a three-stage operation. In 3 a secondary lobectomy was undertaken and in 4 the sputum was reduced from 90 to 30 cc. in twenty-four hours. Lilienthal,[47] who originally was opposed to thoracoplasty in bronchiectasis, recently has reported some very good results following this procedure. Brauer[31] feels that thoracoplasty is the best method of collapsing the lung, as the maximum amount of collapse is thus obtained. Hedblom emphasizes that thoracoplasty should be reserved for those cases of undoubted bronchiectasis. In cases complicated by multiple and multilocular abscesses the procedure is attended with a high mortality. Considerable improvements following thoracoplasty have been reported by Edwards,[48] Duken[5] and McGregor.[43] Sauerbruch,[4] who previously performed a number of thoracoplasties, in a recent contribution concluded that thoracoplasty in bronchiectasis is of no value except in the cases of so-called "retraction bronchiectasis." He states that the failure to obtain results in the other types of bronchiectasis can be understood when one considers that the

bronchi of a bronchiectatic lung cannot be compressed even by a pressure of 80 to 100 pounds. As has been described under the heading of Pathology, bronchi, especially those of the larger diameter become markedly thickened, fibrosed, and may even become calcareous, so that relatively little collapse can be expected following these various procedures. Undoubtedly if desirable results are to be obtained, they can be obtained only in early cases in which there is relatively little change in the bronchi.

Operations on the phrenic nerve, such as division or evulsion of the nerve, have been advocated in bronchiectasis. Very striking therapeutic results have been reported by Rist,[21] Chauffard and Ravina,[49] Brauer,[31] McGregor,[43] Harrington[50] and Davies.[51] Brauer[31] advocates phrenicotomy, because it is less radical than thoracoplasty and is of especial value when the bronchiectasis is limited to the lower lobe and is not extensive. Harrington[50] advocates this operation as a preliminary operation to a more extensive collapse operation. Davies[51] reported 5 cases of bronchiectasis in which a phrenico-exairesis was performed, distinct benefit being obtained in three.

Lobectomy.—Because of the relatively poor results obtained by the drainage of bronchiectatic cavities and also attempted collapse, extirpation of the involved lobe has been performed in a large number of cases. Lenhartz[52] first advocated lobectomy in bronchiectasis. Heidenhain[53] was the first to successfully remove a lobe of the lung for bronchiectasis, following which a bronchial fistula persisted, however. Since this pioneer work, the number of cases so treated has increased considerably. In 1914, Meyer[54] was able to collect 16 cases of bronchiectasis in which a lobectomy was done, with a mortality of 50 per cent. Lilienthal,[55] in 1922, was able to collect from the literature only 30 cases in which a resection of the lung had been performed for suppurative bronchiectasis. He reports 31 cases of bronchiectasis in which a lobectomy was either performed or intended. In 14 of these, in which a single lobe was removed for disease limited to that lobe, 6 died, a mortality of 42.8 per cent. In 10 cases, in which the disease was not limited to a single lobe and in which the operative procedure entailed the removal of more than a single lobe, there were 7 deaths (mortality, 70 per cent). In the remaining 7 cases a lobectomy was attempted but could not be completed, an exploration only being done. Five of these patients died, although none of them died on the operating table. All but 2 of the completed cases were cured. One patient still had productive cough and sputum which had no odor. Lilienthal,[56] five years later, reported the results obtained in 34 cases in which lobectomy was performed by him, in some cases one lobe, in others two lobes, and in still others the entire lung, was removed. There were 7 patients (20 per cent) which were perfectly well. He makes a plea for this method of treatment. Graham,[57] in 1923,

collected 45 cases of bronchiectasis from the literature in which a lobectomy had been performed. Twenty-five of this number had died, giving a total operative mortality of 52 per cent. He reported 3 cases of bronchiectasis in which a lobectomy had been performed by him. Two of the patients died following the second stage; in the third case the operation was successful and resulted in a cure. Of the 48 cases, including the 3 reported by Graham, only 8 could be considered as successes (17 per cent). Because of the high mortality obtained in cases of bronchiectasis treated by lobectomy, Graham[58] advocated cautery pneumectomy in chronic suppurative bronchitis. Subsequently he[59] reported 45 cases of various types of chronic pulmonary suppuration in which a cautery pneumectomy was performed. There was an immediate mortality of 6.6 per cent and a late mortality of 11.2 per cent within a period of three years. Sixty-nine per cent of these cases were free from symptoms. Ten of these still have bronchial fistula. Robinson[60] reported 7 cases of bronchiectasis in which lobectomy was performed, with 3 deaths. Hansen[45] reported 4 cases with one death. Recently, Brunn[61] reported 6 cases in which lobectomy was performed, 5 of which were for bronchiectasis, with one death.

As a less radical procedure, Garre,[62] in 1902, advocated bringing the diseased lobe, in bronchiectasis, outside the chest wall and suturing it to the chest wall, in order to produce a shrinking of the lung. In a case in which this procedure was performed it became necessary to open the lobe and later remove it. Whittemore[36] reported 5 cases in which this procedure was performed. Of these 2 were completely cured, one was improved, one developed pneumonia on the tenth day and died, and the fifth patient, who was operated upon only six weeks before the report, was making a good convalescence. In those cases of bronchiectasis in which the process is limited to a single lobe and in which the symptoms are severe enough to justify the performance of a lobectomy, the greatest amount of relief is obtained by this operation, as it permits a complete removal of the diseased process. Because, however, over half of the cases of bronchiectasis are bilateral and because of the high mortality in bronchiectasis, varying from 10 to 50 per cent, the procedure is applicable to relatively few cases.

Medical Treatment.—Ever since the condition of bronchiectasis was first described by Laennec,[63] the treatment has been largely medical, or conservative, even though conservative therapy has been more or less unsuccessful and unsatisfactory. The introduction of postural drainage by Quincke,[64] in 1898, was one of the most noteworthy advances made up to that time. In addition to postural drainage, which is of distinct value in all cases of chronic pulmonary suppuration, various other conservative measures have been employed in cases of bronchiectasis. Recently, Weinberger[65] has reported a case treated only by postural drainage, which treatment

resulted in a practical cure. Intratracheal injection of antiseptic fluids has been more or less unsatisfactory. The substances used have been menthol, iodoform and creosote. One can realize how ineffective the medical treatment of bronchiectasis has been only after consulting some of the standard textbooks on medicine and noting the large number of drugs which have been used in the treatment of this condition. At the present time the medical treatment of bronchiectasis consists primarily of postural drainage, the intratracheal injection of various medications, and, in certain continental clinics, dehydration. The latter, the "thirst cure," consists of reducing the intake of fluids by the patient, which results in a definite diminution in the amount of sputum. Recently Schott,[10] and Guillemot and Michaux[66] have reported beneficial results obtained by the thirst cure. Vaccine therapy has been employed by Steinmeyer and Kathe[11] in bronchiectasis, with absolutely no changes. Whittemore[36] is very emphatic in condemning the medical treatment of bronchiectasis. He states, "I do not believe that irrigation of the bronchial tree or the injection of medicated oil has any bearing on curing the condition."

Since the first introduction of iodized oil into the tracheobronchial tree by Sicard and Forestier[34] in 1922, iodized oils, especially lipiodol, have been used in a large number of cases. The procedure has been used most extensively as a diagnostic one, but a number of the observers have observed that patients filled with iodized oil also were improved following the introduction of the oil. Such beneficial effects have been noticed by Lenk and Haslinger,[35] Moeller and Magnus,[67] Sgalitzer,[68] and others.[69–82] The beneficial effects obtained by repeated intrabronchial introductions of iodized oil in bronchiectasis have been mentioned in a previous publication.[33] Belfield and Rolnick[83] have shown that iodized oil, when injected into infected seminal vesicles, exerts a direct bactericidal effect. Recently, Ransohoff and Heiman[84] have reported 5 cases of empyema in which iodized oil used primarily as a contrast substance caused a rapid healing and closing of the thoracic wounds. In each of the 5 cases Dakin's solution had been employed, according to the technique of Carrell without any apparent results.

There is some question concerning the manner in which the oil exerts a beneficial effect in bronchiectasis. The author has found, following the intratracheal introduction of iodized oil, a progressive diminution in the number of organisms contained in the sputum. This parallels the improvement in the patient's condition clinically. Whether this is due to a bactericidal effect of the iodized oil or whether it is due to displacement of the bronchial secretions is not known. The author believes that the bactericidal action is the more important of the two.

In contrast to these beneficial results obtained following the introduction of iodized oil into the tracheobronchial tree, other

observers have been unable to obtain any therapeutic effects. Neuswanger[85] smeared agar plates with lipiodol and the following organisms: Bacillus coli, streptococcus, hemolyticus and Staphylococcus aureus. As the organisms grew well, even in close proximity to the oil, Neuswanger concluded that lipiodol was neither bactericidal nor bacteristatic. Archibald and Brown[86] mixed lipiodol with sputum. This mixture was then plated on various culture media. In each instance a profuse growth of organisms resulted. They concluded that the oil was not bactericidal. These experiments were performed *in vitro*, however, and the results obtained are not comparable to those obtained clinically. In the author's own experiments he has been able to show repeatedly that following the introduction of oil into the tracheobronchial tree the number of organisms contained within the sputum as determined by actual count per cubic centimeter decreased progressively. In a previously reported case, this decrease in a number of organisms following introduction of iodized oil is definitely shown.[87]

Is the intrabronchial injection of iodized oil safe and justifiable? Before such a procedure should be performed, either as a diagnostic or a therapeutic measure, one must be convinced that the procedure is not without danger, even though the therapeutic or diagnostic effects be desirable. Since the first introduction of iodized oil into the tracheobronchial tree by "Sicard" and Forestier,[31] in 1912, thousands of patients have been filled with iodized oil by hundreds of different observers, with few untoward results. In 1927, Pritchard, Whyte and Gordon[79] reported a series of over a thousand cases in which bronchography had been used. The author has employed bronchography, either as a diagnostic or therapeutic measure, in over 1500 instances. The greater majority of these fillings have been performed for therapeusis. In the author's series there has never been any untoward reaction. In 6 cases there was evidence of iodism, varying from a slight rhinitis to a rather severe erythematous rash. All the reactions disappeared within forty-eight hours. None of the reactions were at any time alarming. In addition to the clinical there is considerable experimental and pathological evidence of the innocuousness of the intratracheal introduction of iodized oil. Sicard and Forestier,[34, 88] in a large series of animals, were unable to demonstrate any pathologic changes in the bronchi or lung following the introduction of lipiodol. Brauer[89] injected iodopin into the lungs of patients with advanced paralysis or carcinoma, and at autopsy found no evidence of irritation from the iodized oil. Pinkerton,[90] in determining the reaction of the lung to various oils and fats, found that the iodized oils which are used clinically produce practically no reaction in the lungs of animals in contrast to animal oils, which cause an intense pulmonary reaction. Sullivan, Friedbacher and McKinley[91] administered repeated

doses of iodized oil intrabronchially to dogs over long periods of time. The amount of oil employed was relatively greater than the amounts used to fill human beings, as the average dose given to a dog at each filling was 10 cc. The number of fillings varied from 4 to 9. At autopsy, no gross change was demonstrable. Microscopically, there was "in some cases a small amount of fibrosis and, in occasional areas toward the periphery, was chronic passive congestion." Fried and Whitaker,[92] working with cats, introduced iodized oil in amounts varying from 1 to 10 cc. They found that if the oil did not exceed 3 or 4 cc. the animal was not disturbed. In no instances, even in those animals receiving large doses of the oil, was there any evidence of inflammatory change in the lung, but doses exceeding 1.5 cc. of the oil per kilogram body weight was not well tolerated by the animal. Peiper and Klose,[93] on the other hand, conclude, from their experimental work with animals, that the introduction of iodized oil into the trachea is dangerous, as they were able to produce very severe changes in the lungs of rabbits following the introduction of 20 cc. of oil. That their results can be disregarded is self-evident, because of the exceedingly large amounts of oil given to such relatively small animals, the doses being distinctly out of proportion to that given to the human being. Sicard and Forestier,[94] in over 5000 intratracheal injections of iodized oil, observed no untoward effects.

Severe iodine reactions have been reported by Belote[95] and O'Donovan.[96] Miller and Eglee[97] observed 2 cases of iodism, one of which consisted of a very acute toxic erythemia associated with generalized edema. Blumberg[98] advises against the use of iodized oil in cases of hyperthyroidism, kidney or heart lesions and patients inclined to iodism. Deleterious effects following the use of iodized oil in cases of pulmonary tuberculosis have been reported by Aumonte, Leurat, Secousse and Caussimon,[99] Archibald and Brown,[86] Lichtwitz[100] and Ballon.[101] The author agrees with the above observers that iodized oil should be used very cautiously in pulmonary tuberculosis, especially in parenchymatous variety. He has had good results in the fibroid type of tuberculosis, in which the patient is suffering more from the secondary infection of his cavities than from the tuberculous process. Such a case is reported in a previous publication.[87]

As has been stated previously, in the author's series of cases no untoward reactions have been observed, aside from the 6 instances of iodism. In this series of 1500 bronchographies, 112 cases of bronchiectasis were treated by repeated introductions of iodized oil into the tracheobronchial tree. The largest number of fillings received by any one patient was sixteen. The diagnosis of bronchiectasis was made in each case by the fluoroscopic observation of the mode of filling of the bronchi. Roentgenograms were made for confirmation and record. That the fluoroscopic observation of the lung during the filling of the alveoli and the observation of

the mode of filling of the bronchi is more important than the interpretation of the radiographic plate has been stressed elsewhere.[33, 87, 102] In the cases so treated a definite improvement was noted in each one. In 35 cases (32 per cent), there was complete relief of all symptoms, yielding a symptomatic cure, even though there still remained radiographic evidence of bronchial dilatation. In 4 cases not only was symptomatic relief obtained, but also the dilatation of the bronchi, as determined radiographically disappeared. In these cases undoubtedly there was no organic change in the wall of the bronchi but merely a functional dilatation of the bronchi which disappeared following the control of the infection. In the remaining patients, the improvement was so marked that none of the patients cared to interrupt the treatment. In 41 cases (36 per cent) symptomatic relief was obtained, but following an acute respiratory infection there was a return of some cough with a slight amount of sputum. This was, however, never as severe as before the introduction of iodized oil. These symptoms responded quickly to one or two subsequent treatments. In the remaining 36 (32 per cent), improvement was marked. The patients are still under treatment, and still have some cough or sputum or both. Invariably the improvement was evidenced by a decrease in the amount of sputum, a disappearance of the odor of the sputum, if such had been present, an increase in the appetite, and a definite increase in weight, often amounting to as much as 20 to 50 pounds. Any fever which had been present disappeared, and the patient presented an entirely different appearance.

From these results it can be seen that distinct benefit can be obtained in bronchiectasis from repeated intrabronchial injections of iodized oil. The author does not feel that iodized oil is a panacea for all cases of bronchiectasis, but those cases in which there is relatively little pathology or a bilateral process, as well as other cases in which a surgical procedure is not indicated, may be greatly benefited and possibly even cured by the repeated introductions of iodized oil.

It is still too early to say what the ultimate result will be in these cases. Whether the dilated bronchi and cavities will become filled with granulation tissue, and later fibrose, is still unknown. The fact that the patient can be symptomatically cured after a series of from 1 to 10 injections makes it seem advisable to attempt the procedure in all cases of bronchiectasis before resorting to surgery. If the introduction of the oil can be performed in a way which is not difficult for the physician nor unpleasant to the patient, one is justified in employing it in all cases of bronchiectasis, even the earliest, where, undoubtedly, the conservative therapy offers the most. The method which the author has used in his entire series is the "passive" technique, which has been described in detail in previous

publications.[33, 87, 102] Briefly, it consists of anesthetizing the anterior pillars of the pharynx, which abolishes the swallowing reflex. Because of the abolition of the swallowing reflex, swallowing is impossible, and the larynx, which normally rises during deglutition to lie beneath the epiglottis and the base of the tongue, remains immovable. The iodized oil taken into the mouth is then aspirated into the trachea and bronchi. The "passive" technique has definite advantages over the other techniques. It is extremely easy to perform; it permits of the fluoroscopic observation of the mode of filling of the bronchi, and is not at all unpleasant for the patient. In the entire series of patients so treated, no patient ever objected to a refill. It is self-evident that if complicated and cumbersome methods are to be employed, bronchography will be performed in relatively few cases, thereby precluding its use as a therapeutic measure in most cases, as well as a diagnostic procedure in the early cases of bronchiectasis giving a rather atypical history—the patient with "chronic bronchitis."

Conclusions.—1. Bronchiectasis is one of the, if not the, most frequent chronic pulmonary affections.

2. The etiology of bronchiectasis is varied. Chronic bronchitis, influenza, and nasal sinusitis are the most frequent causative agents.

3. About 90 per cent of a series of individuals suffering from chronic bronchitis and recurring attacks of acute bronchitis showed evidence of bronchial dilatation.

4. The symptoms and signs of bronchiectasis as described in textbooks represent a late stage of the condition.

5. The Roentgen ray visualization of the tracheobronchial tree following the intratracheal introduction of iodized oil permits the early diagnosis in bronchiectasis.

6. Bronchiectasis limited to a single lobe is ideally treated by extirpation of the involved lobe. Because of the frequent bilateral involvement and the high mortality resulting from such a procedure, relatively few cases can be treated. The cautery pneumectomy of Graham is the method of choice.

7. The medical or conservative therapy in bronchiectasis has been unsatisfactory heretofore. Postural drainage is, however, of distinct benefit.

8. The repeated intratracheal introduction of iodized oil in cases of bronchiectasis is of distinct therapeutic value. The results of 1500 bronchographies are reported. One hundred and twelve cases of bronchiectasis were treated. Thirty-two per cent were symptomatically cured; 12 per cent of the number showed radiographic evidence of cure. Thirty-six per cent obtained symptomatic relief, but following an acute respiratory infection had a temporary relapse. Thirty-two per cent were improved, and are still under treatment.

9. The "passive" method of introducing the iodized oil is the method of choice because of its simplicity and ease of performance.

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ABSCESS OF THE LUNG: A BACTERIOLOGIC STUDY BASED ON ONE HUNDRED AND EIGHTEEN CASES.

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Many excellent studies on the etiology of abscess of the lung are recorded in medical literature. A number of them are concerned with the mechanism of transportation of the infectious agent to the lung. Hartwell[1] in 1920, Lambert and Miller[2] in 1924 and Ermatinger[3] in 1928 have reported on cultures taken from the pus of pulmonary abscess cases. The last paper cited is chiefly concerned with this particular phase of the subject.

This article presents a bacteriologic study of the pus collected directly from the bronchus of 118 cases of pulmonary abscess, by means of the bronchoscope. I believe that cultures so obtained, more nearly represent the true bacterial flora present in these lesions than do those made from washed sputums. Cultures made at postmortem are hardly representative, for reasons tersely expressed by Hasslinger and Sternberg.[4] This method is perhaps inferior to that of taking cultures from the abscess cavity directly, at open operation. However, this is not often feasible. In this series of cases about 25 per cent were referred to the surgeon for external drainage. Whenever the opportunity presented itself to take cultures at open operation and the interval between the last culture made from bronchoscopically collected pus and the surgical operation was not too great, such cultures were made. There was practical but not absolute agreement between the two sorts of cultures.

The Clinical Material. The material was obtained from the Chevalier Jackson Bronchoscopic Clinic and from Dr. John B. Flick, of the Service of Dr. John H. Gibbon, Jefferson Hospital. The pulmonary abscesses from which pus was collected for bacteriologic examination, represented both acute and chronic lesions. Most of the patients were in the third and fourth decade. The youngest patient was three and a half years of age, and the oldest was sixty-three years. The abscesses followed tonsillectomy, 40; extraction of teeth, 9; surgical operation other than those enumerated, 12; acute respiratory infections, 16; pneumonia, 17; pleurisy, 1, and of questionable origin, 23.

Technique. The material was collected by the bronchoscopist in the following manner: The larynx was exposed by means of a laryngoscope and a bronchoscope was then introduced through it into the tracheobronchial tree. An aspirator which could reach into the bronchus was passed through the bronchoscope and the pus aspirated directly, from the area of infection. Certain observations were made to determine whether bacteria were carried down into the tracheobronchial tree from the pharynx during the introduction

of the instrument. This has been discussed in a previous paper.[5] When the opportunity afforded itself, cultures were taken from the pus of the abscess cavity at surgical operation.

Smears of the bronchial pus were made and stained by Gram's method (Burke's modification) and examined microscopically. Then a portion of the pus was inoculated into a 1 per cent dextrose hormone broth and another portion, plated upon human blood, agar plates. The titer of the media used, ranged between pH 7.6 and pH 7.8. The cultures were incubated at 37.5° C., and examined at the end of forty-eight and seventy-two hours and appropriate transplants were made. Such cultural, biologic and serologic methods deemed necessary, were employed to identify the organisms. Certain organisms were inoculated into animals. When pneumococcus was suspected in the smears, a mouse was inoculated.

Every specimen of pus was subjected to dark-field examination. This was especially intended to disclose the presence and morphologic characteristics of the spirochetes. Fontana's stain and certain of the aniline dyes were also employed for this purpose. In the early cases studied, no systematic attempt was made to culture anaërobes, but lately a portion of pus has been routinely inoculated into deep tubes of glucose (1 per cent) cysteine hydrochlorid (0.1 per cent) agar previously heated to expel oxygen. These were sealed with equal parts, by weight, of paraffin and white vaseline. They were incubated from three to five days at 37.5° C. At the end of this time, the tubes were fractured, by applying a hot rod to a circumferential file mark etched on the tube. Colonies were picked and transferred as the necessity for further study arose.

Results. The accompanying table exhibits the kind of bacteria and the number of times each organism was isolated from the lungs

INCIDENCE OF BACTERIA IN PUS FROM LUNG ABSCESSES ASPIRATED BRONCHOSCOPICALLY.

Streptococcus	Hemolyticus	34	93
	Viridans	44	
	Nonhemolyticus	15	
Micrococcus catarrhalis			61
Pneumococcus			50
Bacillus influenzæ			41
Staphylococcus albus			39
Staphylococcus aureus			22
Diphtheroid bacilli			29
Spirochetes			25
Fusiform bacilli			25
Micrococcus tetragenus			22
Micrococcus pharyngis siccus			9
Friedländer group			6
Bacillus pyocyaneus			2
Diplococcus flavus			4
Bacillus proteus			2
Bacillus bronchisepticus			2
Bacillus coli communis			1
Yeasts			1
Unidentified			17
Total			451

of abscess cases. Of the 118 cases of pulmonary abscess, 20 were studied by anaërobic methods. Anaërobic streptococci were obtained in 14 of the cultures and Staphylococcus parvulus, in 8 of them. Fifteen other anaërobic organisms were obtained. They were chiefly rods; some were fusiform in character and a few had the morphologic characteristics of the spirilla. All cases of tuberculosis have been excluded. In this report the diphtheroid bacilli and the Friedländer group of organisms are reported as groups rather than as individual organisms. In the individual case usually more than one organism was isolated and occasionally 7 or 8 were recovered.

Comment on Individual Organisms. In this series of cases of pulmonary abscess, the streptococci (79 per cent) were of the most frequent occurrence. Of these the viridans type was present most often and nonhemolytic streptococcus was the most infrequent. The abscesses from which hemolytic streptococci were isolated were usually acute and practically all of these patients were very ill. Anaërobic streptococci were the commonest of the strictly anaërobic microörganisms recovered from cultures made by such methods. A microörganism somewhat allied to the streptococcus, the pneumococcus, was present in 42 per cent of the cases. A large percentage of these organisms were typed and the majority of them were Type IV pneumococcus. Type I pneumococcus did not occur in this series.

Both Ermatinger[3] and Hartwell[1] have called attention to the frequency and importance of Staphylococcus aureus in the pus of pulmonary abscess cases. In my series of cultures it occurred in 19 per cent of the cases. Staphylococcus albus (31 per cent) had a much higher rate of occurrence than the former bacterium. Many of the aureus type of staphylococci were hemolytic when grown on blood plates. Like the hemolytic streptococci they produced acute lesions and were associated with severe systemic reactions. From anaërobic cultures a minute, gram negative staphylococcus was isolated on eight occasions. This organism morphologically and culturally conformed to the description of Staphylococcus parvulus of Veillon and Zuber.[6]

The frequence of Bacillus influenzæ (34 per cent) is of interest chiefly because of the many controversies this organism has engendered with regard to its rôle as the etiologic factor of influenza. Certainly, in this instance it was often isolated from patients who gave no history of having had that disease. Yet when one carefully observed blood plates heavily peppered with influenza colonies, and few other organisms, there arose a strong presumption that this organism has very definite pathogenic properties.

Fusiform bacilli and spirochetes were encountered in 22 per cent of the cases. The organisms were identified for the most part by their morphology and motility in the dark-field examination and by smears stained by Fontana's method or with Sterling's aniline gentian violet. I consider aniline gentian violet by far the best aniline

dye with which to study the morphologic detail of these organisms. It stains intensely, so that granules, particularly those in the fusiform bacilli, are well demonstrated.

The spirochetes studied exhibited two types of motility, a lashing type and a boring or corkscrew motility. The organisms varied in length, thickness and in the number of their spirals and in the amplitude and depth of their spirals. Cultures (Noguchi[7]) were made to recover the spirochetes. The results were variable and fraught with many failures. However, on a few occasions impure cultures were obtained. Their outstanding character was the extremely fetid odor which they produced.

I concur with those who believe that the spirochetes found in pulmonary abscess are not of a single kind and that most likely they represent a variety of organisms more or less closely allied. It is worthy of comment that a few of these fusilospirochetal cases had no hematemesis; the sputum was not particularly foul and the patients were not exceedingly ill. Then another peculiarity between the finding of spirochetes and the history of the abscess, is the fact that occasionally a pulmonary abscess followed a surgical operation in a remote part of the body. For example, spirochetes were recovered from a lung abscess which followed a prostatectomy performed under general anesthesia.

Bacillus pyocyaneus was recovered in two instances; once in an abscess following pneumonia and again in an abscess following an osteomyelitis of the jaw bone. On two occasions organisms resembling Bacillus bronchisepticus in all respects, were isolated. These organisms have been reported by Walker[8] in human lesions of the upper respiratory tract. Various other aërobic and anaërobic microörganisms are listed. Most of them seem to warrant no special comment. Among the anaërobic bacteria there were numerous rod-shaped organisms, some had branching forms, others clubbed forms and still others contained granules. They grew very slowly. Some are still under investigation and others were not identified. They included a few cocci and rods.

Discussion. If one scans the table of bacteria isolated in this group of cases, one is impressed with the marked similarity between these microörganisms and those common to the mouth and upper respiratory tract. It is not the purpose of this paper to enter upon a discussion of the mechanism by which pulmonary abscess is produced but it seems justifiable to conclude that if aspiration of mouth bacteria be not the cause of abscess of the lung, the bacteria are at least the potential source of further infection. This point is important and ought not to be neglected in any consideration of the etiology and development of pulmonary abscess.

Since most abscess cavities are infected with a variety of bacteria it is hardly fair to assume that any one of them is the etiologic factor. The mere presence of an organism in an abscess cavity, even though it be a virulent one, is insufficient evidence for ascribing to it a

causative rôle. That the organisms are for the most part pyogenic in nature and contribute to the underlying cause, be it tissue damage from infarction or infection, there seems little doubt. It is admitted too, that among the many organisms present, one or more may be the exciting cause.

In some instances this study furnished me with an opportunity to take repeated cultures on the same individual, over periods of weeks and months. There were almost constant changes in the bacterial flora. It is true that such changes were not marked in character but nevertheless they represent some alteration in the microbic content of the pus. To illustrate the observation, the findings are recorded in a few cases. The original cultures of J. J. contained Streptococcus hemolyticus, Diplococcus pneumoniæ, Staphylococcus albus, Diphtheroid bacilli, spirochetes and fusiform bacilli. A month later Micrococcus catarrhalis was found, but the diphtheroid organisms were no longer present in cultures. M. K. had pus removed bronchoscopically on November 3, 1928. The cultures contained Streptococcus viridans, Micrococcus catarrhalis, Bacillus influenzæ and a Gram negative, nonmotile rod, which produce an opaque glistening abundant chrome yellow growth on potato. On March 28, 1929, pus from the same patient when cultured yielded Staphylococcus albus, Micrococcus tetragenus, Streptococcus viridans and a Diphtheroid bacillus. H. C. who had an abscess, had on September 24, 1928, in cultures seeded from aspirated pus, Streptococcus viridans, Bacillus influenzæ and a Diphtheroid bacillus. Cultures made on October 18, 1928, contained Streptococcus viridans, Bacillus influenzæ and Micrococcus catarrhalis and a further bacteriologic study on November 8, 1928, disclosed the pneumococcus, Bacillus influenzæ, Streptococcus nonhemolyticus and Micrococcus catarrhalis.

One might raise certain objections here. It might be assumed that the organisms not found on a first or second culture were so few, that they failed to grow or others were so numerous, that they were inhibited from growing. Such a condition is possible but then one cannot lose sight of the fact that if this be the case, the numerical disproportion between the several organisms very likely existed in the abscess cavity. I believe that such changes in bacterial flora further substantiate the points already made.

Further evidence is lent by the presence of fusiform bacilli and spirochetes in some of these cases. With the exception of the lesions they produce in the preputial sac and the vagina, which consideration can be dismissed in this instance, the common habitat of these organisms is in the mouth, about teeth and in tonsillar crypts. When such an infection takes place in the lung, it is fair to assume for both anatomic and bacteriologic reasons, that the infection came from the mouth. If we have an abscess following a prostatectomy, which was performed under general anesthesia, there is no further room for doubt as to how these organisms gained entrance into the

lung. For here we have an instance of infection with micro-organisms whose common habitat is the mouth, following an operation in a region, the prostate, remote from the lung. But perhaps one case is insufficient upon which to base an argument. Two more of like nature occurred in this series. One abscess followed drainage of a gall bladder and another followed a forceps delivery. Both were performed under general anesthesia and both were spirochetal abscesses.

Summary. Pus from 118 pulmonary abscesses was studied bacteriologically. Streptococci were most commonly found in these cultures. Staphylococci, pneumococci, Bacillus influenzæ, Fusiform bacilli, spirochetes, various anaërobes and other organisms, some unidentified, were also recovered. It is concluded that the organisms found in pulmonary abscess are similar, for the most part, to those found normally in the mouth and upper respiratory tract. It is not possible, ordinarily, to pick out any one organism as the etiologic factor, but it is believed that many of the organisms found in the abscess cavity gained entrance from the mouth and upper respiratory tract through the air passages.

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PARATYPHOID–ENTERITIDIS MENINGITIS.

Report of an Additional Case Due to Bacillus Enteritidis.

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and

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The following is a report of a case of meningitis due to a Bacillus enteritidis, which report is preceded by an analysis of the literature on the subject.

There are numerous reports on record of the finding of bacilli of the paratyphoid group in the cerebrospinal fluid. In fifteen of these cases the organisms may be accepted as members of that group. We have accepted only cases in which identification was based on indisputable cultural or serologic evidence.

The distribution of cases was as follows: Germany, 4; Italy, 3; Austria, 2; British Isles, 2; France, 2; Syria, 1; and the United States, 1. The only case in the United States previous to the one here reported was also in Philadelphia.

The ages of the patients varied from eleven days to twenty-five years and could be divided into three age groups: a year or less, 8 cases; six to eleven years, 4 cases; twenty to twenty-five years, 3 cases. In 2 cases the age was not given.

The cerebrospinal fluid was purulent in 10 instances, clear in 4, and in 1 the nature was not reported. In our case the turbidity was largely due to bacilli. This may have been true also in some of the cases reported as purulent in which the cells were not actually counted.

Blood cultures were positive in all cases in which they were made, with the exception of the case here reported.

The duration of meningeal symptoms in the fatal cases varied from one day to fifteen days, most of the deaths occurring within the first week. The disease was fatal in all cases in children under one year of age.

All of the 8 cases which came to autopsy showed purulent meningitis, 5 had enteritis, and 1 had pyelitis. Table I gives the significant data in these cases.

Report of an Additional Case. P. K., a female, aged twelve months, colored, was admitted to the service of Dr. J. C. Gittings, in the hospital of the University of Pennsylvania, on July 22, 1927, in a convulsion. According to the child's mother, it had had a normal birth and had never been ill, except for a slight cold the preceding winter. She had never had any gastrointestinal disturbance.

While playing in the street on the morning of the onset of her illness she seemed perfectly well, and shortly after 11 A.M. she fell into a normal sleep, from which she wakened at 6.15 P.M. with a sudden cry, and developed a clonic convulsion of the left upper and lower limb, which later became generalized. The convulsions persisted almost continuously until her death at 5 P.M. on July 23, twenty-three hours after the onset of the symptoms.

On admission, her weight was 19½ pounds; temperature, 103° (axillary); pulse, 160; respirations, 40.

The convulsions started usually in the left limbs, and from there spread to include all the extremities and the face. The eyes presented a rapid lateral nystagmus during the convulsions, but were quiet and in the normal position during the intervals. The seizures were almost continuous, and were controlled only by chloroform anesthesia.

The head was moderately retracted, the parietal bosses large and the fontanelles open. There was no hyperemia nor bulging of the ear drums. The heart and lungs were clear and the abdomen showed only moderate

TABLE I.

Reported by.	Age of patient.	Spinal fluid, character.	Spinal fluid culture.	Blood culture.	Duration of life after meningitis symptoms.	Autopsy.†
Arts and Boese	5 mos.	Purulent; polys. and lymphs.	B. para B or B. enteritidis	Not done	24 hrs. ?	Purulent meningitis; internal hydrocephalus; catarrhal enteritis.
	7 wks.	Purulent	Unidentified	+	4 days	Purulent meningitis; internal hydrocephalus; acute gastroenteritis.
Symmers and Wilson	4 mos.	Purulent	B. para B or B. enteritidis	Not done	?	Purulent meningitis.
Eckert	8 mos.	Purulent	B. para A	+	6 days	Purulent meningitis; enteritis nodularis.
Tolmer and Weisenbach	25 yrs.	Purulent; polys. predominate	B. para A	Not done	2 days	Purulent meningitis; enteritis.
Walterhofer	20 yrs.	?	B. para B	+	Recovery	
Hundeshagen	3 mos.	Purulent; polys. predominate	B. para B	Not done	12 days	Purulent meningitis, purulent pyelitis.
Lesne	25 yrs.	Purulent fluid	B. para B	+	Recovery	
Smith and Aberd	5 wks.	Turbid fluid; 90% polys.	B. enteritidis	+	7 days	Purulent meningitis; enteritis.
Caronia and Auricchio	9 yrs.	Clear	B. para A*	+	Recovery	
	6 yrs.	Clear	B. para B*	+	Recovery	
Voight	11 days	Many polys.	B. para B	+	4 days	Purulent meningitis.
Brahdy	13 mos.	8000 w. b. c.; polys. predom.	B. para A	Not done	5 days	None.
Stuart and Krikorian	11 yrs.	Clear fluid; few lymphs.	B. enteritidis	Not done	14 days	None.
Pansini	9 yrs.	Increased pressure; 7 to 8 lymphs. per high-power field	B. para A	Not done	15 days	None.
Lynch and Shelburne	12 mos.	140 cells, 80% polys., myriads or organisms	B. enteritidis	Negative postmortem	23 hrs.	None.

* Organisms discovered during routine spinal fluid examinations in case of enteric fever.
† Only positive findings recorded. Special attention was paid to evidences of pathology of the spleen and intestines.

distention. There was no Kernig, Babinski or Brudzinski sign, but all the normal reflexes were increased.

The urine examination was entirely negative. The blood count showed: Red blood cells, 4,160,000; white blood cells, 6100; neutrophils, 57 per cent; lymphocytes, 41 per cent; large mononuclears, 2 per cent. The blood Wassermann reaction was negative.

Lumbar puncture on admission revealed a clear fluid with 140 cells, of which 80 per cent were neutrophils and 20 per cent lymphocytes. After fifteen hours another lumbar puncture showed a ground-glass appearance of the fluid with no change in the cell count, the turbidity being caused by myriads of organisms, which were easily detected in the counting chamber. As the nature of the process was still in doubt at this time, 15 cc. of anti-meningococcus serum were administered intraspinally, with no relief of symptoms.

Necropsy was refused, but a postmortem pericardial puncture revealed an entirely unsuspected large collection of serosanguinous fluid, which on culture proved to be sterile. Culture of heart's blood was also sterile.

Cultural Studies. The cultures of the cerebrospinal fluid gave a luxuriant growth of bacilli with the characteristics of B. enteritidis.

Morphology. An actively motile Gram-negative rod, averaging about 1 to 3.5 mikra by 0.4 mikra, and staining readily with aniline dyes. There is no spore formation.

Cultures. The organism grows readily on ordinary culture media. Agar surface colonies are delicate gray, translucent, finely granular colonies, about 1 to 2 mm. in diameter, entire, smooth, convex and having thin margins. Deep colonies are smaller and tend to be lanceolate. The growth on agar slants is abundant, reaching its maximum in forty-eight hours. The consistency is butyrous. Gelatin is not liquefied, but there is abundant growth along the line of inoculation as well as on the surface. Broth gives a heavy turbidity with a pellicle forming on the third to the eighth day, at which time a heavy granular sediment appears. On Löffler's blood serum the surface growth is abundant and cream-colored, with no digestion of the media. On potato there is a yellowish, nonspreading surface growth. Litmus milk is acidified in twenty-four hours, becoming alkaline in three or four days. There is no coagulation. Proteolysis starts in about seventy-two hours, and is almost complete in ten days. There is no hemolysis on blood-agar plates. Nitrates are reduced to nitrites. No indol is formed in peptone media. Hydrogen sulphid is produced. Acid and gas are formed in the following 1 per cent carbohydrate broths: dextrose, levulose, arabinose, inosite, dulcite, rhamnose, mannose, mannite, zylose, maltose and galactose. There is no fermentation of inulin, dextrin, raffinose, lactose, salicin nor saccharose.

Thermal Death Point. Salt solution suspensions of twenty-four-hour agar-slant cultures were killed by heating at 55° C. for thirty minutes.

Pathogenicity. Rabbits were infected by intravenous injection of 0.5 cc. of a twenty-four-hour broth culture, and the organisms were

recovered from the intestine at autopsy. There was no evidence of meningitis in the rabbit, and meningeal cultures were negative. Subconjunctival inoculation of a rabbit produced an abscess, which cleared up in three weeks. There was no evidence of meningitis in this animal.

The cultural and biologic characteristics of this organism place it in the paratyphoid-enteritidis group. The members of this group from which it cannot be differentiated by cultural methods alone are B. paratyphosus B, B. enteritidis, B. suipestifer and B. aertrycke (de Nobile).

Serologic Studies. Agglutination tests were performed between the organism here reported, No. 20249, and the following known strains:

B. paratyphosus A, Mear's strain, originally from the Hygienic Laboratory.

B. paratyphosus B, Cool's strain, originally from the Hygienic Laboratory.

B. ærtrycke, de Nobile, No. 633 American Type Culture Collection.

B. suipestifer, No. 214, American Type Culture Collection.

B. enteritidis, No. 210, American Type Culture Collection.

The tests included, first, the reaction between the unknown organism No. 20249, and sera specific for the various members of the group; second, the reaction between the various members of the group and a serum specific for No. 20249; third, the reaction of certain members of the group and the specific 20249 serum, after absorption of agglutinins from the latter by the various organisms tested.

Technique. The agglutinating sera for B. paratyphosus A and B were obtained from the laboratories of H. K. Mulford Company. The other antisera were prepared by the injection of killed cultures of the homologous organisms into rabbits. These antigens were salt solution suspensions of twenty-four-hour agar-slant cultures, killed by heating for thirty minutes at 60° C. The antigens for agglutination were prepared by growing the organisms for four days in nutrient bouillon with daily subculture, after which they were centrifuged at high speed for ten minutes. The supernatant fluid was then pipetted off, and the organisms were suspended in salt solution. These living antigens were used for the agglutination tests. After the agglutination tests had been set up they were incubated for two hours at 55° C. in the water bath. Readings were made at the end of this time, and again after eighteen hours in the ice box.

The technique for the agglutinin absorption tests was as follows: twenty-four-hour cultures on agar slants, after three daily subcultures, were stirred directly into 3 cc. of the immune serum to be tested, until a suspension of a standard density was obtained. The suspension was then incubated at 37° C. for two hours, centrifuga-

lized, and the clear, supernatant fluid was pipetted off and diluted as shown in the table. The balance of the test was the same as that with unabsorbed serum.

TABLE II.—AGGLUTINATION TESTS.

Immune serum.	Antigen.	Dilution of immune serum.								
		1 in 20.	40.	80.	160.	320.	640.	1280.	2560.	5120
20249*	20249	+++	+++	+++	+++	++	++	++	0	0
	B. enteritidis	+++	+++	++	++	+	0	0	0	0
	B. ærtrycke	++	++	++	+	0	0	0	0	0
	B. suipestifer	+	0	0	0	0	0	0	0	0
B. enteritidis . .	B. enteritidis	+++	+++	+++	+++	++	++	+	0	0
	20249	+++	+++	++	+	+	+	0	0	0
B. ærtrycke . .	B. ærtrycke	+++	+++	+++	+++	++	++	0	0	0
	20249	+++	+++	++	++	+	+	+	0	0
B. suipestifer . .	B. suipestifer	+++	+++	++	++	++	+	0	0	0
	20249	0	0	0	0	0	0	0	0	0
B. paratyphosus A	B. para A	+++	+++	+++	+++	+++	++	+	0	0
	20249	++	0	0	0	0	0	0	0	0
B. paratyphosus B	B. para B	+++	+++	+++	+++	+++	++	+	0	0
	20249	++	++	+	0	0	0	0	0	0

* 20249 is the organism isolated from the cerebrospinal fluid of the case here reported.

Results of Agglutination Tests. Table II gives the agglutination reactions of sera of animals immunized against the organisms in the first column, and tested with the organisms in the second. Our culture No. 20249 is agglutinated by antienteritidis serum, antiærtrycke serum and antiparatyphosus B serum. 20249-Antiserum agglutinates B. ærtrycke and B. enteritidis.

TABLE III.—AGGLUTININ ABSORPTION TESTS WITH IMMUNE SERUM OF B. PARATYPHOSUS B ABSORBED BY ANTIGENS NO. 20249 AND B. PARATYPHOSUS B.

Absorbing antigen.	Antigen.	Dilution of immune serum.						
		1 in 20.	40.	80.	160.	320.	640.	1280.
B. paratyphosus B	B. paratyphosus B	0	0	0	0	0	0	0
	20249	0	0	0	0	0	0	0
20249	20249	0	0	0	0	0	0	0
	B. paratyphosus B	+++	+++	+++	+++	+++	++	+

Table III shows the results of an absorption test performed to exclude the identity of No. 20249 and B. paratyphosus B., the commonest of the three test organisms mentioned above. This test reveals the fact that B. paratyphosus B could absorb all antibody from antiparatyphosus B serum, while No. 20249 could only absorb its own nonspecific agglutinin from that serum. It, therefore, did not disturb the titer of the serum for its own specific organism. This shows that No. 20249 is not B. paratyphosus B.

TABLE IV.—AGGLUTININ ABSORPTION TEST WITH IMMUNE SERUM OF NO. 20249 ABSORBED BY ANTIGENS OF OTHER STRAINS.

Absorbing antigen.	Antigen.	Dilution of immune serum.								
		1 in 20.	40.	80.	160.	320.	640.	1280.	2560.	5120.
20249	20249	0	0	0	0	0	0	0	0	0
	B. enteritidis	+	0	0	0	0	0	0	0	0
	B. ærtrycke	+	0	0	0	0	0	0	0	0
B. enteritidis . .	B. enteritidis	0	0	0	0	0	0	0	0	0
	20249	+	+	+	0	0	0	0	0	0
	B. ærtrycke	0	0	0	0	0	0	0	0	0
B. ærtrycke . .	B. ærtrycke	0	0	0	0	0	0	0	0	0
	20249	+++	+++	+++	++	++	++	0	0	0
	B. enteritidis	+++	++	++	++	++	++	+	0	0

Table IV gives the results of agglutinin absorption tests performed with No. 20249 serum treated with No. 20249, B. ærtrycke, and B. enteritidis antigen, each of the sera being tested, after absorption, with each of the three organisms.

This test shows that organism No. 20249 takes out all agglutinin from its own serum, and takes out nearly all the specific enteritidis antibody from the antienteritidis serum. It takes out no agglutinin from antiærtrycke serum. From this, with the cultural observations, we conclude that the organism here reported is identic with B. enteritidis of Gaertner.

Summary. A review of the literature reveals 15 previous cases of meningitis from which bacilli of the paratyphoid-enteritidis group were isolated, and a sixteenth case is here reported.

Most of the cases occurred in children.

All the cases aged a year or less died, including the present case.

In most of the cases the fluid was purulent, or showed a predominance of polymorphonuclear neutrophils.

In all the previously reported cases in which blood culture was made, it was positive. In our case postmortem blood culture was negative.

Conclusions. Meningitis due to bacilli of the paratyphoid-enteritidis group is a serious condition, usually fatal in the very young. It should be suspected whenever Gram-negative motile rods are found in the cerebrospinal fluid.

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REVIEWS.

LE CANCER. By GUSTAV ROUSSY, with the collaboration of ROGER LEROUX and MAURICE WOLF. Pp. 846; 280 illustrations, and many colored plates, charts and tabulations in the text. Paris: Masson & Co., 1929.

THIS very impressive volume is a second completely revised and reset edition of Volume II of the Fifth Fasciculus of the "Nouveau Traité de Médecine by Roger," Widal and Teissier.

It is a work of really magnificent appearance, though formidable in size. It is beautifully illustrated with photographs, photomicrographs and colored plates. Unfortunately, however, it is printed upon a very highly glazed paper in order that the cuts may show to best advantage, which is bad for the reader on account of the reflections of light from the pages, which tire the eyes.

It covers the entire subject of oncology—history, philosophy, etiology, morbid anatomy, histology, experimentation, statistics, treatment, tumors of the lower animals, tumors of plants, and so forth, and, in general, the treatment is quite full and satisfactory.

Some American readers may experience difficulty with the nomenclature, which is different from that to which they are accustomed.

J. McF.

ESOPHAGEAL OBSTRUCTION, ITS PATHOLOGY, DIAGNOSIS AND TREATMENT. By A. LAWRENCE ABEL, M.S. (LOND.), F.R.C.S. (ENG.), Assistant Surgeon to the Cancer Hospital, London; Surgeon to the Kensington General Hospital; Assistant Surgeon to the Woolwich War Memorial Hospital; Surgeon to the London Locke Hospital. Pp. 220, including full bibliography for each chapter; 132 illustrations and 2 color plates. New York: Oxford University Press, American Branch, 1929. Price, $9.00.

THE book is unique in that the whole subject of esophageal disease is presented in relation to its most important symptom, namely, obstruction. It is well written, interesting, and apparently based on a wide surgical experience and clinical knowledge. An exhaustive bibliography appended to each chapter shows wide reference to the literature although, occasionally, an important contribution seems to have escaped the author. The anatomic, embryologic, physiologic and bacteriological considerations in esophageal disease are

presented. General diagnosis including instrumentarium is considered. Roentgen ray and direct esophagoscopic examination are stressed as the most important and only reliable means of arriving at the correct diagnosis in esophageal disease. Medical, Roentgen ray and surgical methods of treatment of esophageal disease are presented, but from the standpoint of the American clinician many of our well established procedures are not properly evaluated, and are discarded. Esophageal constrictions due to congenital malformations, acute obstruction including foreign bodies; cardiospasm and neuropathic affections of the esophagus, and obstruction due to extrinsic pressure are given adequate consideration. Diverticulum, pharyngo-esophageal, is considered under pathology, diagnosis and treatment. Diverticulum of the esophagus proper; chronic esophagitis, including simple ulcer, simple tumor, varices, granulomata (tuberculosis, syphilis, actinomycosis), and simple strictures of the esophagus are given three chapters. Of particular interest are the four last chapters of the book devoted to cancer of the esophagus, pathology, diagnosis, palliative treatment and radical treatment. The author strongly emphasizes the fact that the only hope of curing cancer of the esophagus lies in early diagnosis, which can be made only by direct examination with the esophagoscope. In referring to the radical cure by surgical excision the author states, "Cancer of the esophagus is so fatal that in the absence of any contraindication such as metastases, or extreme emaciation radical removal should always be attempted." The book is distinctly surgical in its point ef view and is a most important contribution to the literature of osophageal disease. G. T.

SELECTED READINGS IN PATHOLOGY FROM HIPPOCRATES TO VIRCHOW. Edited by ESMOND R. LONG, Professor of Pathology, University of Chicago. Pp. 301; 25 illustrations. Springfield, Illinois and Baltimore, Maryland: Charles C. Thomas, 1929. Price, $4.00.

THOSE who cherish Camac's "Epoch Making Contributions to Medicine" as an easy and tempting way of getting back to certain important original sources were delighted to hear that Long was to follow up his History of Pathology with translations of excerpts from the works of the master writers of medicine. We use the word medicine advisedly for the history of pathology in its broadest sense is so interwoven with the history of medicine that in this volume, for example, only two or three out of the thirty-six selections belong strictly in the domain of morbid anatomy. Thus the editor has quite properly included such clinicopathologic treatises as Corvisart's "Diseases of the Heart," Laennec's immortal "Traité de l'Auscultation Mediate," Bright's "Reports of Medical Cases," and so on. The chronological order has been followed and original

passages, varying from 2 to 26 pages in length, have been selected either for their intrinsic historical importance or as representative samples of "lengthy volumes which in their entirety were of unusual influence." Following Hippocrates, Celsus, Galen and Paul of Ægina, Rhazes represents the Arabic influence, and William of Saliceto the mediæval period. In the Renaissance, we have Benivieni, Fracastor and Fernel; while Severinus, Tulp, Wepfer and Sylvius share with Harvey in the seventeenth century. Lancisi, Ruysch and Astruc lead up to the great Morgagni, while Hunter, Baillie and Bichat usher in the nineteenth century. Here the great English and French pathoclinicians are liberally represented, while our own Horner, Gerhard and Gross precede the two master pathologists, Rokitansky and Virchow.

It is a rather melancholy fact for pathologists that the last contribution considered worthy of inclusion in this series was written over seventy years ago, a longer period than had elapsed between any of the previous selections back to the fifteenth century. E. K.

MINOR SURGERY. By FREDERICK CHRISTOPHER, M.D., F.A.C.S. Pp. 694; 465 illustrations. Philadelphia: W. B. Saunders Company, 1929. Price, $8.00.

THE author has presented to his readers a most instructive and comprehensive treatment of true minor surgery. It has been some time since the reviewer has had the pleasure of writing a criticism which has such little adverse criticism in it. He ventures to express the opinion that this is the most thorough, instructive, up-to-date and interesting work of the sort that it has been his pleasure to read in years. The book contains a world of information most aptly imparted to one who cares to read. The story is admirably presented and each subject is covered well. Senior surgeon, assistant surgeons, interns and students all can profit by having this book at hand throughout their daily work. E. E.

VARICOSE VEINS. By H. O. MCPHEETERS, M.D., F.A.C.S. Pp. 208; 35 illustrations. Philadelphia: F. A. Davis Company, 1929. Price, $3.50.

IN this little volume the author has made a résumé of a most thorough investigation of the literature throughout the world and combined it with his own experience in the care and treatment of some 800 cases of varicose veins. He discusses the embryology, anatomy, etiology and pathology of this very common condition and points out the shortcomings of surgery and the advantages of the

injection treatment. This treatment is outlined in great detail, giving the drugs, technique, induration, contraindications and complications as well as the results to be expected. The book should be read by every surgeon and internist for it presents the entire subject in a most comprehensive and convincing manner.

The volume is a well appointed, nicely written and well-illustrated example of a good piece of work. E. E.

La Terapia Epatica e Le Sue Applicazioni con Particolare Riguardo All' Anemia Perniciosa. By Paola Introzzi. Pp. 75. Bologne: L. Cappelli, 1929.

Following an interesting retrospect of the use of liver in therapeutics, the author considers the various ways in which it may exert its beneficial effect in pernicious anemia. His choice—a poor one, we believe—of the antihemolytic action of the liver is apparently based on Ferrata's teaching that the embryonic megaloblast is replaced by the normal erythroblast simultaneously with the formation of liver cells! In treating pernicious anemia, he has had good results with extracts of lymph nodes and considers that the active principle is not specific to the liver, but may be found in lymph nodes, kidney, heart and voluntary muscle. E. K.

An Outline of Endocrinology. By W. M. Crofton, B.A., M.D. Second edition. Pp. 163; 53 illustrations. New York: William Wood & Co., 1929. Price, $3.00.

Realizing that a medical textbook is partly out of date when it first appears, in the first edition, the author left blank pages for notes at the end of the book. In the present edition instead of revision, the notes are supplied for these pages. The book is sane, reasonably up to date and contains a surprising amount of worthwhile information within its small content.

E. K.

An Introduction to the Study of Physic. By William Heberden (1710–1801). Pp. 159; 7 illustrations. New York: Paul B. Hoeber, Inc., 1929. Price, $2.00.

Few are more to be envied than the keen bibliophile whom circumstances permit to give free rein to his hobby. At the moment, rare in these days, when in addition to this he is permitted to pick up some unsuspected rarity for a mere trifle, then is he indeed in his seventh heaven. In the prefatory essay of this book, Dr. Crummer, one of our most persistent and successful "nugget" discoverers,

describes how the manuscript of this hitherto unknown work of Heberden's was brought to light. And the "Introduction" is well worth reading today for its own sake. For good measure, a reprint of Heberden's "Some Account of a Disorder of the Breast" is also included, so that we have conveniently at hand the first account of that disease of physicians, angina pectoris. E. K.

STEPHEN HALES, D.D., F.R.S. AN EIGHTEENTH CENTURY BIOGRAPHY. By A. E. CLARK-KENNEDY, M.D., M.R.C.P., Fellow of Corpus Christi College, Cambridge, Assistant Director of the Medical Unit and Assistant Physician to the London Hospital. Pp. 256; 14 illustrations. Cambridge University Press. Sole American Agents New York: The Macmillan Company, 1929.

MOST medical men know, or should know, that Stephen Hales was the first to measure the pressure of the circulating blood and that he successfully combined a profitable religious and scientific career. How many, however, are acquainted with his studies on the growth of bone, the chemistry of respiration and the flow of sap in trees; or with his achievements in ventilation—among the earliest in preventive medicine—or with the part that he played in successfully establishing our colony of Georgia, and in bringing the Wesleys to this country? For those who would like to know more of this interesting character the story is here told in a better and more complete form than can be found elsewhere. E. K.

THE CUSTOM OF COUVADE. By WARREN R. DAWSON, F.R.S.E., Fellow of the Royal Society of Medicine, of the Society of Antiquaries of Scotland and of the Royal Anthropological Institute. Pp. 118; 1 illustration. Manchester, England: Manchester University Press, 1929. Price, 7 shillings and sixpence.

"THE word 'Couvade' is the name applied to a curious and widespread custom that was known in antiquity, and still survives in many parts of the world. According to this custom, the father of a child, at the time of its birth, takes to his bed and behaves generally as though he, and not his wife, were the mother of the infant."

Though more ethnological than strictly medical, this book is sure to interest the inquiring medical mind. Though widespread through primitive races of all ages, including the present, the reason for this curious custom has never been satisfactorily solved. In bringing together a monumental list of examples to provide material for an intelligent discussion of the significance of this interesting problem, the author has furnished a most readable and entertaining volume. E. K.

BOOKS RECEIVED.

NEW BOOKS.

*Diseases Transmitted from Animals to Man.** By THOMAS G. HULL, M.D. Pp. 350; 29 illustrations. Springfield, Ill. Charles C. Thomas, 1930. Price, $5.50.

Grundlagen der ätiologischen Behandlung der Nierenentzündungen. By DR. VIKTOR KOLLERT. Pp. 161. Leipzig and Wien: Franz Deuticke, 1929. Price, M 9.

The Cancer Process. By J. J. M. SHAW, M.A., M.D., F.R.C.S.E. Pp. 16. Edinburgh: E. and S. Livingstone, 1930. Price, 1 shilling.

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*The Immunology of Parasitic Infections.** By WILLIAM H. TALIAFERRO, PH.D. Pp. 414; 28 illustrations. New York: The Century Company, 1929. Price, $6.00.

*The Medical Museum, Based on a New System of Visual Teaching.** By S. H. DAUKES, O.B.E., M.D., D.P.H., D.T.M. and H. Pp. 172; 44 illustrations. London: The Wellcome Foundation, Ltd., 1929.

NEW EDITIONS.

*Incompatibility in Prescriptions and How to Avoid It.** New edition revised and enlarged. By THOMAS STEPHENSON, D.SC., PH.C., F.R.S. (EDIN.), F.C.S. Pp. 61. New York: Paul B. Hoeber, Inc., 1929. Price, $1.50.

Mammalian Physiology. A Course of Practical Exercises. A new edition. By E. G. T. LIDDELL, D.M., and SIR CHARLES SHERRINGTON, O.M., M.D., D.SC. (CANTAB.), F.R.S. Pp. 162; 50 illustrations. Oxford: Clarendon Press, 1929.

A very valuable book for physiological classes in any country.

*The Essentials of Histology.** By SIR EDWARD SHARPEY SCHAFER, F.R.S. Professor of Physiology in the University of Edinburgh. Pp. 628; 758 illustrations. Twelfth edition. Philadelphia: Lea & Febiger, 1929. Price, $5.00.

The Care of the Nose, Throat and Ear. By W. STUART-LOW, F.R.C.S. (ENG.) Pp. 88; 18 illustrations. Second edition. London: Baillière, Tindall & Cox, 1929.

A Textbook of the Practice of Medicine. By Various Authors. Edited by FREDERICK W. PRICE, M.D., F.R.S. (EDIN.). Pp. 1871; 112 illustrations. Third edition. Oxford University Press, 1929.

Bacteriology for Nurses. By HARRY W. CAREY, A.B., M.D. Pp. 282; 44 illustrations. Third edition. Philadelphia: F. A. Davis Company, 1930. Price, $2.25.

* Reviews of titles followed by an asterisk will appear in a later number.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Nasal Spray Method of Administering Hormones of the Ovary and Pituitary Gland.—In 1922 Blumgart suggested the application of pituitrin into the nasal mucosa in order to do away with the necessity of repeated hypodermic injections in the treatment of diabetes insipidus, stating at that time that extracts of the posterior tube of the pituitary are effectively absorbed from the nasal mucosa. PRATT and SMELTZER (*Endocrinology*, 1929, **13**, 320) performed experimental tests upon rats to see if the ovarian hormone is absorbed through the mucous membrane of the nose or the vagina. They found that it was definitely absorbed from these two sites, as well as from the conjunctiva. They report upon a series of patients to whom the ovarian hormone and the active principles of the posterior lobe extracts were given by the mucous membrane of the nose route, utilizing for the application of the substances a small glass nebulizer. They report that applied in this fashion in the nose, the material is completely absorbed without sign of local irritation. When local nasal abnormalities exist, it is possible to make use of the vaginal mucosa. The advantages of the nasal method of administration over hypodermic injections are too obvious to need repetition.

Exhaustion States.—There has been an increase in the exhaustion states in the past ten years. Just why this has occurred has aroused considerable discussion. DOWDEN and JOHNSON (*J. Am. Med. Assn.*, 1929, **93**, 1702) write that four causes have been suggested for this well recognized increase in the loss of a sense of well-being of the present-day generation: (1) The World War and its effects; (2) the 1918 epidemic of influenza and its persistent residuum; (3) the advent of prohibition, and (4) the oversaturation of the atmosphere with carbon

monoxid from the exhausts of automobiles. They have examined 688 patients without specific underlying disease. They note that in these individuals complaining of ease of tiring that there is a reduction in the gastric acidity; that there is a lowered basal metabolism; the blood pressure is diminished; a secondary anemia is common, as is a slow pulse. After an extremely thorough examination of these run-down individuals, they conclude that the exhaustion state arises chiefly from infections of the respiratory tract and from nervous and mental strain. To cure it, the etiologic factor must be removed. Sometimes this is a comparatively simply procedure; at other times it is extremely difficult. Under any circumstance, endocrine therapy, which they recommend, would be of no value unless the etiologic factor responsible for the production of the condition is removed.

The Effect of Guanidine Compounds on Unanesthetized Dogs.—MAJOR and WEBER (*J. Lab. and Clin. Med.*, 1929, **15**, 125) state that when guanidine salts are injected into the experimental animal there is an elevation of blood pressure. Certain observers have reported in unanesthetized animals that there was a fall of pressure. In order to determine this point they observed a series of dogs who were given relatively small doses of *methylguanidine sulphate* when not under the influence of an anesthetic. Blood pressure was raised very strikingly before any toxic symptoms appeared and increase in the pressure was greater in the unanesthetized animal than in the dog under ether.

SURGERY

UNDER THE CHARGE OF

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Pathologic Lesions of the Gall Bladder.—BAUMGARTNER (*Surg., Gynec. and Obst.*, 1929, **49**, 780) claims that there are no characteristic symptoms or clinical data to differentiate the apparently earlier types of cholecystic disease; in the later stages, however, certain characteristic data are present. The clinical features of chronic catarrhal cholecystitis and strawberry gall bladder or cholesterosis were identical. The occurrence of stones in a fairly high percentage of gall bladders showing minimal pathologic change further substantiates the theory that gall bladders may assume a normal appearance between attacks. Chronic fibrous cholecystitis showed a higher incidence of gall-stone colic, jaundice, chills and fever than the groups of chronic catarrhal cholecystitis and strawberry gall bladder. Stones were present in 89 per cent of the cases in this group. Acute and subacute cholecystitis may occur without appreciable increase in temperature or leukocytosis. Gall stones occurred in 96 per cent of the cases. The symptoms of empyemia of the gall bladder vary greatly. The chronic form usually is not accompanied by any grave manifestations. The acute form not

infrequently is fulminating in character. Stones occurred in 96 per cent of these cases also. Gangrene of the gall bladder is associated with marked clinical manifestations. There is marked tenderness and the temperature and leukocyte count are higher than in the acute forms. Stones occurred in 96 per cent. Papillomata occur more frequently than the reported frequency. The single papilloma is friable and easily overlooked. The relation between papilloma and malignancy is problematic. Adenomata always occur in the fundus. The common types of malignant lesions are carcinoma simplex, adenocarcinoma, squamous-cell epithelioma and sarcoma.

Immediate and Eventual Features of Healing in Amputated Bones.—BARBER (*Ann. Surg.*, 1929, **90**, 985) says the same successive stages in bone healing were observed which are characteristic of repair in fractures. These are in order, vascular erosion in bone end and adjacent shaft, consequent molecular disintegration of bone adjoining the site of amputation, rounding of bony stump itself, quiescence in osteoporotic shaft, closure of medullary cavity by cap of bone, which rapidly becomes condensed, restrained production or absence of osteophytes. The time element accords well with the time of appearance of the corresponding phenomena in healing fractures. The original erosion of the amputated end is already well advanced within five or six days of the surgical trauma, even before the marks of the saw cut are obliterated from the bone. Flake-like sequestra undoubtedly occur and probably separate in less than three weeks. In amputation stumps the production of callus is much more restrained than in fractures. The medullary cap is certainly developed from the endosteal and definitive callus.

Radiation in the Treatment of Rectal Cancer.—BIRKLEY (*Ann. Surg.*, 1929, **90**, 1000) writes that efficacy of radiation therapy in the treatment of rectal cancer has been greatly increased by improvement in technique. Reclassification of rectal cancer from the standpoint of the degree of radiosensitivity and of malignancy has resulted in an improved treatment of this disease. Utilization of radical surgery as an adjunct to treatment by radiation therapy is often the method of choice. The effects of treatment of this disease by any single method or combination of methods are greatly enhanced when an early diagnosis has been established. Recognition of the degree of malignancy is suggested as the determining factor in the choice of surgical route, whether abdomino-perineal or perineal if surgery is indicated.

Arsphenamin Dermatitis with Gangrene.—ROBINSON (*Am. J. Syph.*, 1929, **13**, 536) states that this fatal case of arsphenamin dermatitis was the result of neoarsphenamin poisoning and could probably have been avoided if the physician had stopped therapy with the onset of itching. This is the second case of this character within three weeks' time, and the author believes that it should be stressed that neoarsphenamin is sometimes attended with severe and even fatal reactions. In reviewing the literature a case complicated with dry gangrene was noted. All the fingers and two-thirds of the hands were totally mummified.

THERAPEUTICS

UNDER THE CHARGE OF

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Experiences with the Gerson Diet in Pulmonary Tuberculosis.—SCHWALM (*Klin. Wchnschr.*, 1929, **8**, 1941) reports his experiences with the diet recently described and advocated by Gerson from Sauerbruch's Clinic. It was claimed that this diet not only improves but also cures patients with severe forms of tuberculosis. The author, however, observed no beneficial effect on 20 patients. The clinical and Roentgen ray examination of the lungs showed no appreciable improvement. The gain in weight was not different from that of other patients on routine diet. The blood picture and sedimentation rate was also uninfluenced.

The Treatment of Pleuritic Effusions.—HORDER (*Brit. Med. J.*, 1929, p. 605) believes that the successful handling of a case of pleuritic effusion depends on a consideration of the following factors: (1) The cause of the infection; (2) the nature of the effusion; (3) its size; (4) the stage in the disease at which the patient has arrived; (5) the associated condition of the lung; (6) the degree of illness of the patient; (7) the contribution made by the effusion, as such, to the illness. No effort should be spared in making a diagnosis as to the nature of the infection and effusion. An active and inflammatory process in the lung should, on the whole, contraindicate the removal of pleuritic effusion, for the presence of fluid is beneficial in keeping the lung at rest. Of course, the toxic and mechanical influence of the fluid should be considered with judgment. In case the *serous effusion* (tuberculotic) is large or causes respiratory or cardiac embarrassment, it should be tapped at once. If no signs of absorption are present after fourteen days, it should be tapped. Too early and too frequent removal of fluid may spread or cause a flare-up of the underlying pathologic process. Too late interference may leave the lungs permanently collapsed. If there is definite evidence that the lung is diseased, the replacement of the fluid by oxygen should be considered. Because spontaneous absorption or the removal of fluid at the proper time almost always takes care of the effusion, the author believes that the problem of *auto-serotherapy* is "a matter of supererogation." In removing the fluid local anesthesia should be used effectively. The nick of the skin with a sharp scalpel before inserting the needle is advocated. Trocars with cannules are to

be avoided. If the patient feels well there is no limit to the amount to be removed. Drugs injected into the pleura are of doubtful value. After care is important and it should be conservative. In rheumatic effusions, aspiration is seldom necessary. In lymphadenoma and cancer the individual case must determine the care. In case of *purulent effusions* and empyema, the principles of treatment of serous effusions holds, but the time factor is of greater urgency. During the active stage of pneumonia, resection and incision should be postponed, and aspiration should be repeated if necessary. In a considerable number of cases this method suffices. The character of the pus is less important than the general condition of the patient in deciding the choice of treatment. If the active process in the lungs is subsiding and the general condition is satisfactory, incision, rib-resection and drainage is the preferred method. It is very doubtful if irrigation as a routine procedure is justified by results. Irrigation at the time of operation is of questionable value, and in care of pulmonary abscess it certainly should be avoided. The care of the patient should receive special attention. Fresh air, good food, sunlight and ultraviolet rays are beneficial.

"Activated" (Irradiated) Fluorescein in the Treatment of Cancer.—Encouraging results in the treatment of certain types of malignant tumors is reported by COPEMAN, COKE and GOULDESBROUGH (*Brit. Med. J.*, 1929, p. 233). A solution of 2 to 2.5 per cent (occasionally 5 per cent) sodium fluorescein containing 3 per cent sodium bicarbonate was used. Neutral solutions were found to be inactive. The sodium fluorescein had to be activated by Roentgen rays which penetrate a filter of 4 mm. of aluminium to be effective. Because of the fairly moderate penetrating ray used for excitation there was a limit to the depth of the body at which results could be obtained. The most striking cases were those of superficial growth, such as breast carcinomata, sarcomata, malignant glands, bone tumors in thin parts, etc. Apparently the more cellular the tumor the better the results. The routine treatment outlined by the authors is as follows: (1) Paint with fluorescein solution, or administer internally; (2) irradiate with an adequate dosage of Roentgen rays or radium; (3) repeat 1, 2, 3 times, at intervals of a week; (4) allow three weeks rest; (5) repeat the complete cycle, as often as considered desirable. On the seventh day in many instances retrogression of the growth may appear. Progress seems to vary much. Four to six months continuous treatment is necessary before the result can be judged definitely. Large fungating tumors may break down so rapidly as to cause serious toxic effects. Seventy cases of malignant disease ("for the most part stated to be 'inoperable' ") were treated. Eight of the patients apparently recovered, 20 were much improved, 7 are too recent for statement; the others either showed no improvement or died. The most satisfactory response was observed in cases that had not been treated by any method previously. In superficial secondary growth, injection of the tumor with a few drops of fluorescein solution often resulted in rapid disappearance of the growth. Often if fluorescein treatment is used in cases considered inoperable, the induced changes make the case amenable to surgery.

PEDIATRICS

UNDER THE CHARGE OF

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The Period of Infectivity and Serum Prevention of Chickenpox.—GORDON, MEADER (*J. Am. Med. Assn.*, 1929, **93**, 2013) state that preceding the eruption chickenpox is apparently infectious for only a brief period, probably not more than twenty-four hours. Infectivity during convalescence is less prolonged than commonly considered and does not necessarily coincide with the persistence of crusts. It probably lasts only ten days. Convalescent serum furnishes a high degree of protection if secured within one month of the period of the lesions. If the serum is obtained after a longer time it is progressively less efficient and after five months confers immunity only in about one-third of the immunized susceptibles. In their work to corroborate the reported results of the protective action of the serum, they used 10 cc. of a pooled serum from convalescents of from one to two months. The results were very satisfactory. In three outbreaks there were no secondary cases. In another outbreak, one of six immunized susceptibles developed chickenpox. These children were all under eight years of age and 11 were less than four years. The possibility that divided doses might give better results was not upheld on trial. In their experiments 55 of 81 susceptible children or 68 per cent developed chickenpox when serum was not used. It was seen from this that it is not logical to conclude that the absence of infection in the immunized group was entirely due to the use of serum as a certain appreciable proportion seemed to escape infection under all conditions. The duration of immunity is brief. Reëxposure of 12 patients from secondary cases resulted in 2 clinical cases. In administering the serum it was given intramuscularly into the lateral aspect of the thigh. There were no reactions. As far as could be observed the course of the disease in immunized patients was in no way modified nor was the expected incubation time appreciably affected.

The Early Diagnosis of Latent Heredosyphilis.—ALARCON (*Arch. d. Med. des. Enf.*, 1929, **32**, 589) indicates a new clinical guide in the diagnosis of syphilis on the basis of a typical intestinal disorder occurring in children under three months of age. He calls this the transitional dyspepsia of infants. It is characterized by symptoms occurring during the first days of breast feeding. Shortly after feeding regurgitation and hiccough occur which at times may awaken the infant. The intestinal disorder is evidenced by crying. Vomiting is rare in breast-fed infants although frequent in artificial feeding. Acid diarrhea with erythema of the buttocks follows the initial constipation. The author divides the condition into a preliminary stage lasting three weeks, a secondary stage lasting six weeks and a final stage lasting three weeks,

and he feels that the influence of syphilitic septicemia on the nervous system is the most frequent cause. The early onset with the exaggerated symptoms and the prolonged duration are suggestive of the underlying lues.

The Size of the Reacting Area in Intracutaneous Tuberculin Tests.—DICKEY (*Am. J. Dis. Child.*, 1929, **38**, 1155) studied 700 positive reactions to tuberculin. In these he found that the average area of the reaction was about 459 sq. mm. The size of the reaction varied widely in the group studied with the exception of that in very young children and of that in children having phlyctenular conjunctivitis. He observed no difference of the average size of the reaction in girls and in boys. There was a gradual increase in the size of the reaction from the first to the sixth year although this may not mean an increase in the degree of sensitization. Children of Oriental parentage were more sensitive than other racial groups. Children who had had contact with tuberculous persons reacted more strongly than children who gave no such history. He suggests a relationship between sensitivity and the extent of the markings in roentgenograms but he does not feel that there is any relationship between sensitivity and other roentgenologic observations. It was noted that children with phlyctenular conjunctivitis, lymph node, bone and joint tuberculosis reacted more strongly than those with hilar disease although the latter gave slightly stronger reactions than children suffering from an adult type of pulmonary tuberculosis.

Breast Feeding.—GERSTLEY (*Arch. Ped.*, 1929, **46**, 749) in a series of breast-fed babies noted that in each baby the amount taken at individual nursings during the day were quite varied in contradistinction to the statements in textbooks that children take the same amount of food at each nursing. The variability of some of these observations is extreme. Not only varying in amounts at each feeding and thus giving an irregular twenty-four hour total so that no two days were identical. One of the most surprising observations made was the enormous quantity of milk taken by one of the babies at some of his nursings, even during the early months of his life. These observations were checked and were found to have been accurate. It was noted that during the fourth week of age this infant took as much as $8\frac{1}{2}$ to 9 ounces at a nursing. This was an extreme record. Gerstley feels that his figures show that it is impossible to standardize the diets of infants because their intake depends primarily upon their constitutional demands. He feels that this lesson should be remembered in bottle feeding. In this study the amounts of milk taken from each breast of the mother were also determined and in this series there was a greater ouput from the right breasts of the mothers not only in the case of an older child who nursed more vigorously but also in the younger child. The author feels that the stimulus of the nursing infant is a great factor in promoting secretion of milk but there may be individual variations in the breasts themselves.

The Kahn Precipitation Test in Infants and in Early Childhood.—CAFFEE and KREIDEL (*Am. J. Dis. Child.*, 1929, **38**, 1206) feel that the Kahn test is a highly sensitive and specific serologic test in infancy and

early childhood and while it closely parallels the Wassermann reaction it is not identical with it. Positive Wassermann reactions are more easily reversed by antisyphilitic treatment than are positive Kahn reactions. The latter is considerably more sensitive than the former in mothers of syphilitic offspring. It is highly specific in mothers of nonsyphilitic offspring and equals the Wassermann test in this regard. It has decided advantages in simplicity as a laboratory procedure. In their study the authors believe that the Kahn test performed alone would have given somewhat more reliable information than the Wassermann performed alone but the performance of both complement fixation and precipitation test simultaneously on identical serums give more imformation than either test alone and affords a double control in serologic diagnosis.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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Early Syphilis, Results of Treatment in Four Hundred and Forty-four Cases.—CHARGIN and STONE (*Arch Derm. and Syph.*, 1929, **19**, 750) state that while there is no complete agreement among syphilographers on the best single plan of treatment, it is generally accepted that the treatment should be intensive and that the combination of arsphenamin with mercury or bismuth should be used. This constitutes the modern method of antisyphilitic therapy and although it has been employed only for about fifteen years, it has been in use a sufficiently long time to permit the evaluation of results. Chargin and Stone present an analysis of 444 cases of treated early syphilis in the period 1911 to 1926. The criteria of cure in this series and standards involved included the earliness of the stage at which the treatment was started; the use of at least one course of arsphenamine and one course of mercury or bismuth; the freedom from clinical recurrence while under treatment with a negative Wassermann at the end of treatment; observation for a least one and one-half years following the last treatment with no clinical recurrence during this period; and repeated negative Wassermanns during the period of observation. The authors did not examine the spinal fluid in all cases (nor is mention made of physical reëxaminations or special neurologic or cardiac studies, so that to this extent the data for decision as to cure are seriously incomplete). The cases were classified in four groups, primary seronegative cases, 36; primary seropositive cases, 55; early secondary cases, 267; and late secondary cases,

86. The plans of treatment employed were: (1) *The intermittent plan*, regular courses of arsphenamin and mercury or bismuth with alternating periods of rest of one or two months. In this group were 269 patients. (2) *The intensive plan* (Pollitzer), early saturation treatment of the patient with frequent and large doses of arsphenamin followed by a course of mercury or bismuth and concluded by a final course of arsphenamin. This was used in 16 patients. (3) *The mixed injection plan*, using a mixture of neoarsphenamin and mercuric chlorid in courses, with alternating periods of rest. Twenty patients were treated according to this plan. (4) *The continuous plan*, alternating course of arsphenamin and mercury without rest periods for as long as a year. This was used in 55 patients. (5) *The irregular plan*, as the name suggests, was used to designate a group of 85 patients treated without any organized or definite scheme. The term "course" as used by the authors means 6 to 8 injections of arsphenamin and 12 to 15 injections of mercury or bismuth. The dosage varied with the age and weight of the patient, arsphenamin averaging from 0.2 to 0.4 gm. per injection, and mercury or bismuth 1 to 15 cc. of the insoluble preparations (amounts of the salt not given). The majority of the patients in this series were treated with arsphenamin and the heavy metal concurrently, with rest periods between courses. The authors believe that continuous treatment is generally not well borne, and that rest intervals are desirable to permit elimination of accumulated drugs and to avoid toxic effects. In primary seronegative syphilis, 90 per cent of the patients were apparently cured within the inadequate standard accepted by the authors and one-third of the cured patients received but one course of treatment. The authors feel that the important factor in this stage is the early beginning of treatment rather than the amount or method employed, although it is noteworthy that the 4 cases receiving the intensive plan of treatment were all regarded as cures. Fifty-five cases of seropositive primary syphilis were treated, with 61 per cent of cures. Again the majority of cures in this group were in the patients receiving but one or two courses of treatment. The same percentage of cures, that is, 61, was obtained in 267 cases of early secondary syphilis, the majority receiving intermittent treatment and but one or two courses. Intensive treatment was employed in 8 cases with cures in all. Of the 86 patients in the late secondary group, cures were obtained in 45 per cent. A general consideration of treatment based on the number of courses showed surprising results. Cures were obtained in 74 per cent of those patients receiving but one course, 72 per cent for two courses, 54 per cent for three courses, 50 per cent for four courses and 28 per cent for five or more courses. The authors believe this apparent paradox is explainable by the fact that the failure of patients to respond after one or two courses augurs a poor outlook for cure after further treatment. (Are we to interpret that the authors advocate one or two-course treatment as a standard for cure in those patients who would "respond" during that period, or is their use of the term "cure" open to discussion?) Beyond the 100 per cent results achieved with the intensive plan of treatment (16 cases) the plans of treatment appeared equally efficient, cures ranging from 57 to 60 per cent. The authors feel, however, that the patient is benefited by employing a plan that includes rest periods, inasmuch as the chance for cure appears to be in no way diminished.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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Menstrual Disorders Treated by Irradiation of Ovaries and Hypophysis.—It has been known for some time that irradiation of the ovaries and of the hypophysis very often has a definite effect on the menstrual flow and its disorders. FORD and DRIPS (*Radiology*, 1929, **12**, 393) report on the clinical and experimental studies of low-voltage irradiation as conducted at the Mayo Clinic. They state that irradiation of the ovaries or hypophysis has been effective in reëstablishing menstruation in patients in whom prolonged use of organotherapy had been ineffective. A conclusion cannot be drawn as to the comparative efficiency of methods because the cases selected for irradiation were of unusual severity. Irradiation of the hypophysis, occasionally combined with splenic and hepatic irradiation has exerted a temporary regulating effect in 7 cases of severe menorrhagia and metrorrhagia. Relief of dysmenorrhea has been incidental in certain cases of menorrhagia and oligomenorrhea. Of 6 cases treated primarily for dysmenorrhea, relief has been complete in 3 and has lasted for a period of four to six months; improvement occurred in 2 others. Irradiation of ovaries of white rats in various dosages produced no continued influence on the regularity of the estrual cycle. Complete destruction of follicles did not result from dosages up to 2.5-unit skin doses. There was no influence on fertility, except in cases in which there was marked systemic reaction, with irradiation of 50 per cent unit skin doses or below. With the application of $2\frac{1}{2}$-unit skin doses sterility has been produced in 5 of 10 rats. Abnormality in the progeny has not been demonstrated. They state that a consideration of the mechanism by which small amounts of Roentgen rays, acting either on the ovaries or on the hypophysis, are able to reëstablish cyclic menstruation and to relieve sterility would serve only to open theoretic controversy. The harmlessness of irradiation of the ovaries in low dosage seems to them to be sufficiently well established by all pertinent biologic studies and by the numerous instances of normal children being born to women who had previously been irradiated with even much heavier doses than those required in the treatment under consideration.

Results of Treatment of Cervical Cancer.—From the Gynecologic Clinic of the University of Kiel comes a report by CLAUBERG (*Zentralbl. f. Gynäk.*, 1929, **53**, 2339) of 380 cases of carcinoma of the cervix which were seen between January 1, 1917, and September 30, 1922.

Of these cases, 107 were living and free from evidence of carcinoma at the end of five years; therefore, there is an absolute healing rate of 28.2 per cent. Some years ago the result of this clinic for the period of from 1910 to 1916 were reported by Giesecke and the following table which summarizes that report as well as the present series is of great interest:

	1910-16	1917-22
Total number	350	380
Operability, per cent	70.6	54.7
Number operated upon	243	160
Primary mortality, per cent	18.9	13.0
Operable cases:		
1. Wertheim	224	148
Primary mortality, per cent	19.6	14.2
Relative cure, per cent	33.5	43.2
2. Vaginal hysterectomy	19	12
Primary mortality, per cent	10.5	0
Relative cure, per cent	57.9	50.0
3. Irradiation	3	48
Primary mortality, per cent	33	0
Relative cure, per cent	67	43.7
Inoperable cases:		
1. Irradiation[a]	60	150
Primary mortality, per cent	not given	6
Relative cure, per cent	8.3	10.6
2. Operative procedures	43	3
Irradiation	..	2
No treatment	..	17

It is of interest to note that the operability rate has decreased due to the fact that the irradiation percentage has markedly increased. Even though there is a very satisfactory reduction in the operation mortality in the second series this clinic has seen fit to subject an increasing number of patients to irradiation so that while there is still a large number of operations performed, the surgical treatment is becoming less popular as is the case in this country.

OPHTHALMOLOGY

UNDER THE CHARGE OF

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Amaurosis Following Ingestion of Ethylhydrocuprein.—Though ethylhydrocuprein is a quinin derivative and its use in pneumonia is growing, few cases of visual disturbances due to its use have been reported. ALVIS (*Arch. Ophth.*, 1929, **2**, 328) presents a case of sudden amaurosis which must have been due to the disease since its course so resembled quinin amaurosis. In the course of three days the woman, aged twenty-two years, had been given 58 grains of ethylhydrocuprein at the rate of 4 grains every five hours. During the third night she lost her power to distinguish color and by morning she was unable to distinguish light. Two hours later she was entirely blind, the pupils

widely dilated and fixed. Five hours later ophthalmoscopic examination showed widely dilated pupils, disks very pale with slightly blurred margins, retinal arteries practically obliterated because they were so narrowly contracted; small and thread-like retinal veins. In the right macula there was a cherry spot in the moderately edematous retina. There was no such in the left. When seen by Alvis ten days later there was no change, though she could perceive light. Two months later the fundus was the same except that the cherry spot had disappeared and the edema was gradually clearing. She was able to count fingers at a distance of 8 feet in a fairly wide field. Four months after the attack the pupils were wide and reacted sluggishly to light. The patient saw everything through a purple haze which prevented differentiation of colors. Vision in either eye was 20/75. The visual fields were restricted between 15 and 30 degrees. As soon as the diagnosis of ethylhydrocuprein poisoning was made nitrites were given in increasing doses. Potassium iodid and pilocarpin was given for diaphoresis. Hot applications were made to the eyes. Later increasing doses of strychnin were administered. The author concluded that amaurosis from ethylhydrocuprein can occur in a severe form, though extremely rarely and that the treatment is without influence on the condition. Some permanent disability follows even mild cases of ethylhydrocuprein or quinin poisoning, varying with the severity of the intoxication.

Ocular Lesions in Tularemia.—There are four clinical types of tularemia in one of which conjunctivitis is the primary lesion and there is involvement of the regional lymph glands. This form usually shows multiple, small, discrete ulcers of the palpebral conjunctiva with indurated margins and yellow, necrotic plugs. There is pronounced chemosis and swelling of the lids and mucoid discharge. Swelling and tenderness of the regional lymph glands is present, the fever is intermittent, the convalescence prolonged. JUDD (*Arch. Ophth.*, 1929, **2**, 300) reports 2 cases of the ocular type of tularemia. The first case was typical, the second atypical for swelling of the axillary glands preceded the ocular trouble and dendritic keratitis appeared; this latter has apparently not previously been reported. The eyes in the first case soon recovered, being treated with instillations of 1 per cent mercurochrome-220 soluble, corrosive mercuric chlorid ointment 1 to 2000 and hot applications, and moderate doses of salicylates. The second case, when seen, presented conjunctival congestion and circumcorneal injection. There were several dotlike areas on the upper, inner quadrant which stained with flourescein; in the pupillary area there were several thin nebula. A mild iritis was present. There was no swelling of the regional lymph glands. The eye was treated with hot, moist applications, atropin, 1 per cent mercurochrome, corrosive mercuric chlorid ointment and was kept bandaged. The dots had coalesced by the fourth day, forming a typical dendritic ulcer on the upper, inner part and across the cornea below the pupil. Slight inflammatory infiltration in the superficial layers of the stroma beneath the epithelial lesion, but no keratitic precipitates, were shown by the slit lamp. There were no st ins by the tenth day. Vision which at first had been 20/100, became 20/50 with correction. There has been no recurrence.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF
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Vertigo.—The symptoms of vertigo are well known, yet much remains for the clinician to study and learn, and for the scientist to survey and explain. Patients who have had both labyrinths completely removed or who have bilateral auditory nerve tumors involving the whole of each eighth nerve and deaf-mutes who have complete loss of function of the vestibular nerves, do not suffer from vertigo. On the other hand, normal persons can become dizzy without any physical disturbance of the labyrinth—reminding us that every case of vertigo is not necessarily labyrinthine in origin. Defining vertigo "as the state of consciousness of a false sense of orientation of ourselves in relation to our environment," SCOTT (*J. Laryngol. and Otol.*, 1929, **44**, 429) after mentioning labyrinthitis, otitis media and otosclerosis as aural conditions which not uncommonly give rise to giddiness, emphasizes the association of recurrent vertigo with inefficiency of the Eustachian tubal mechanism. In discussing vertigo among aviators, he states that all pilots should be capable of inflating both Eustachian tubes by Valsalva's method, or of opening them by the act of swallowing before they should risk high flying. Other causes of vertigo, such as reflexes from conditions affecting the fifth nerve, syphilis, and disseminated sclerosis, are enumerated.

Pathologic Changes in Tonsils. A Study of Ten Thousand Pairs of Tonsils, with Special Reference to the Presence of Cartilage, Bone, Tuberculosis and Bodies Suggestive of Actinomycosis.—WILKINSON (*Arch. Otolaryngol.*, 1929, **10**, 127) makes a comprehensive statistical and analytical report based on the findings of a histopathologic study of ten thousand pairs of tonsils removed consecutively at the Mayo Clinic from 4616 females and 5884 males with a true average or mean age of 33.56 years and a standard deviation, or spread of the material, of 17.7 years (probable error of 0.1 year). Following fixation in a 10 per cent solution of formaldehyde, each tonsil was bisected horizontally and a frozen section from the bisected surface of each tonsil was mounted and stained with hematoxylin and eosin. After a complete compilation of the data in the 10,000 cases, it was found that all tonsils showed evidence of chronic infection, if the presence of leukocytes in the crypts and ulceration of the epithelium are indications of infection. However, in only 14.27 per cent of tonsils were there "pathologic changes of bizarre types." Cartilage and bone occurred in various grades and proportions in 11.21 per cent, cartilage predominating. Fibrosis was relatively increased in those sections showing cartilage and bone. The author believes that chronic infection is a great and definite factor in the production of fibrosis, bone and cartilage although he recognizes that

fibrosis can increase independently of infection and in direct relationship to age. Actinomycosis-like granules were encountered in 1.77 per cent. Tuberculosis of the diffuse type had an incidence of 0.52 per cent, in 0.17 per cent of which the involvement was bilateral. Trichinæ were identified in 0.06 per cent of the extirpated tonsils, occurring in the capsular or septal tissues. The author concludes that "there is sufficient pathologic change of interest in the tonsils to warrant routine microscopic examination of removed tonsils.

Pathogenesis of Sepsis Following Angina. Histologic Observations of the Material from 26 Patients of Professor Claus, Berlin.—In the microscopic examination of the tissues from 26 cases of postanginal sepsis—11 of which came to postmortem and in the other 15, surgically removed tonsils were available for study—BURCHARDT (*Ztschr. f. Hals-, Nasen- u. Ohrenheilk.*, 1929, **23**, 97) stressed the common occurrence of perivascular infiltration, which began in the tonsillar tissue and could be traced (in the necropsical material) to the larger regional veins. In five instances in which the presence of sepsis was not entirely convincing the vascular lumina were clear, although a lymphangitis was observed. Some cases exhibited lymphadenitis and suppurative thrombophlebitis. Often all the layers of the bloodvessel walls showed inflammatory changes. On one occasion medical disintegration was found in the absence of demonstrable intimal inflammation or thrombosis. The author believes that the presence or absence of a thrombophlebitis plays a minor rôle insofar as the actual genesis of postanginal sepsis is concerned.

RADIOLOGY

UNDER THE CHARGE OF

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Radium Therapy.—The entire March issue of *The Radiological Review* (1929, **51**, 93-140) is devoted to radium therapy. In the first paper PFAHLER relates his experience in the treatment of *cancer of the mouth*. It is painless at the time of application, though it causes soreness and swelling of the mouth at the height of the radiation effect; it requires no anesthetic, no hospitalization, and produces neither mutilation nor constitutional symptoms: in tongue cases the function of the tongue is preserved; it usually causes metastatic lymph nodes to disappear. Of a total of 56 advanced intraoral cancers with glandular metastasis treated during the past three years, 36, or 64 per cent, are living; 23, or 41 per cent, are clinically cured, and 13 are still under treatment.

HENRIQUEZ has had success in the treatment of *hypertension*. The method consists in the application of 50 mg. of radium to each side of the skull at a point just in front of and a little above the external auditory meatus. The radium is filtered by 2 mm. of brass and is at a distance of 1 inch from the skin. One hour's application, repeated weekly until the pressure falls, is considered best. Diastolic pressure has been lowered over 20 mm. in certain cases, the enlarged heart has been reduced in size, and the patients have improved subjectively.

Plantar warts were treated successfully by COSTOLOW in 20 cases. In 15 only a single treatment was required.

Of 9 cases of *adenocarcinoma of the cervical canal*, treated by SCHREINER, 1 is alive and well after eight years; 1 died in four years from intercurrent disease after being well for three years; 1 died after one year of palliation, and the remainder died of recurrence and metastasis. In 50 per cent of the operable cases of *cancer of the fundus* the patients are healed alive and well after more than five years: in the inoperable cases no patient survived five years.

SWANBERG has used a modified cervical applicator for the Regaud technique in *cancer of the cervix*. He believes that surgical treatment should be abandoned since better results are secured by irradiation. Statistics show that 72 per cent of cervical cancers, representing all stages, are living one year after irradiation, with 27 per cent free from the disease after five or six years.

According to MURPHY and MURPHY, all patients with *cancer of the skin* can be cured by radium, without pain, loss of time or disfigurement, if properly irradiated while the lesion is confined to the integument.

TYLER reports a case of *osteogenic sarcoma* of the humerus treated by radium and Roentgen rays, in which the destroyed bone was largely regenerated and the patient is in apparent good health after one year.

LENTH regards radium therapy as the treatment of choice in *epithelioma of the lip*, because there is less inconvenience, loss of function and disfigurement than from any other form of treatment and it yields a higher percentage of cures. Palpable lymph glands should be treated by radium and resected if unimproved.

Roentgen Ray Diagnosis of Lesions of the Small Intestine.—For examination of the small bowel SOPER (*Am. J. Roent. and Rad. Therap.*, 1929, **12**, 107) employs a special technique: (1) The patient must be examined in the upright posture. (2) Abnormalities in the small intestinal pattern should be sought for from two and a half to six hours after the opaque meal is given. They are often demonstrable about the time the last part of the barium meal leaves the stomach. (3) Make films of suspicious areas at once, and continue to watch for other anomalies. Shadows are likely to be evanescent; the examiner should remember that he is searching for evidence of partial and not complete obstruction.

The shadows produced by peritoneal tuberculosis are bizarre and irregular in character and portray the various scattered dilatations and contractures of intestinal loops. Metastatic carcinoma of the peritoneum and intestine produces a similar picture. Primary cancer of the small bowel may produce a pseudodiverticulum but it is more irregular than a true diverticulum, and the shadow of the latter persists

for a much longer time. Shadows resulting from adhesions are instructive; atypical patterns may be found in nearly all patients who have been subjected to abdominal section. Strong bands of adhesions may cause periodical attacks of partial obstruction with dilatation of the loops. A gas-bubble above the barium level is a frequent finding. Twenty-four-hour stasis in the ileum must be regarded as pathologic; of course, its presence twenty-four hours after the meal may be due to pyloric obstruction. Extraälimentary growths may cause obstruction or distortion by pressure or adhesions.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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Les Tumerus du Quatrième Ventricule et le Syndrome Cerebelleux de la Ligne Mediane.—VAN BOGAERT and MARTIN (*Revue Neurologique* 1928, **2**, 431) present 12 cases of tumors of the fourth ventricle with a clinical study for the purpose of developing diagnostic criteria. They conclude from their observations that the fourth ventricle tumors have a very rapid onset with rapid early development. The headache is usually very precocious with cramps in the neck, vomiting, vestibular or tonic attacks and certain modifications of attitude and epigastric or segmental pain and symptoms of the involvement of the vermis, (ataxia, asynergia, dysmetria) very often unilateral. The papillary edema appears and the patient adopts his typical attitude. This is due to a block of the cerebrospinal circulation. Later there appear bulbar symptoms, syncope, pseudoanginal crises, pseudoasthma, episthotonic crises, irregularity of the pulse and of the respiration, attacks of apnea, generalized crises of sweating with sometimes glycosuria. The function of the cranial nerves is rarely involved and disturbances in these cases have no localizing value. The complete evolution of the cases is very rapid, from six to ten months. Very rapid death is frequent, at times on the operating table. Ventricular puncture will relieve the pressure on the bulb and may allow the patient to survive. In detail the interesting symptomatology is the early onset of paroxysmal headache and painful radiation to the neck, the shoulders or the arms. These headaches are accompanied by two phenomena, an objective rigidity of the muscles of the neck and sometimes of the trapezius with an attitude of hyperflexion and often a lateral deflection of the head in an attempt to reëstablish the hydraulic equilibrium of the posterior cerebral fossa. This is due to a blockage of the cerebrospinal circulation, which can be demonstrated and was demonstrated in 3 of their cases by graphic

determination of the cerebrospinal-fluid pressure. In these cases the blockage was partial, was increased by hyperextension and decreased by flexion of the neck. Hence they consider this position of flexion as representing a reaction in an attempt to reëstablish the hydraulic equilibrium in the cranium. They found that brisk movements of the head may give rise to crises of variable gravity, from simple minor disturbances to a fatal syncope with apnea. In addition they find early disturbances of the genitourinary functions which they consider as symptoms of involvement of the median fasciculus. Disturbances of gait are not marked in the early stages but are usually mildly present throughout the inferior members and coördination is conserved in the arms. Following the early symptoms we have a state that is characterized by a syndrome of general hypertension and by the appearance of localizing signs. This begins very rapidly and a double papillary edema is quickly developed, hence we may have labyrinthian excitation, transitory diplopias, digestive disturbances, etc. The marked hypertension of the posterior cerebral fossa is manifested by ventriculography which shows marked internal hydrocephalus, and clinically it is shown by the symptoms of meningeal irritation. The tumors affect the subcerebellar pontine quadrilateral. They are directly adjacent to the main afferent and efferent paths of the cerebellum, the lateral and median bundles of Reil and the vermis, hence the symptoms of cerebellar involvement and especially of involvement of the vermis are present. A large majority of the patients complain of disturbances of equilibrium in gait and station. The progression is characteristic and retropulsion is frequent. The asynergia of Babinski and decomposition of movements are present in many cases in a classic manner. One sees in many cases hypermetria, slowing of the preterminal movements, intention tremor, and adiadochokinesis. Disturbances of writing, reading and speech are generally absent and proprioceptive reflex disturbances are exceptional. Bárány tests are not of value because they are rendered uncertain by the hypertension of the posterior fossa. The function of regulation of the muscle tone is much disturbed and to this disturbance is attributed the tonic attacks (cerebellar fits of Jackson) and the hypotonicity of the muscles and loss of tendon reflexes. The tonic attacks do not occur in all tumors of the fourth ventricle or in all of the median cerebellar line but when they are observed they have great localizing value and are symptoms of serious import. They have been found in lesions of other locations such as tumors of the angle, of the peduncle and of the pons. The picture is that of tonic contraction with hyperextension of the entire body, hyperextension and pronation with adduction of the superior members, trismus, Cheyne-Stokes respiration and irregularity of pulse. The face is pale, the tendon reflexes are abolished, the corneal reflex and pupillary reflexes to light are frequently absent. The head may be deviated to the opposite side or to the side of the body where flexion is manifested. The eyes are turned upward, at times laterally to the side where hyperextension is most marked. The rectal temperature is not increased during the crisis. Consciousness may be abolished but not always completely so. The attack may predominate on one side of the body and give rise to a turning of the body which causes the paroxysmal syndrome of torsion about the longitudinal axis of the body. This syndrome has been

observed in other lesions of the cerebellum. The combination of tonic attacks of torsion and the opisthotonic crises with hyperactivity and confusional states has been confused with hysteria. Between the attacks the tendon reflexes are abolished and many of the patients present hypertonicity with the abolition or enfeeblement of certain tendon responses. This abolition of reflexes is explained by the influence of the tumors of the fourth ventricle on the rubrospinal and reticulospinal tracts while the corticospinal inhibition persists. Certain minor symptoms and very rare symptoms have been observed. The signs of grave concern are the tonic attacks, the bulbar attacks and the negative Quackenstadt tests. The presence of one of these symptoms indicates the urgency of intervention. The phase of decline is characterized by the presence of the increase in the bulbar symptoms and is frequently followed very shortly with death. The bulbar symptoms are primarily tachycardia of extreme irregularity, alternation vasoconstriction and vasodilation of the face, dyspnea with polypnea or Cheyne-Stokes respiration, polyuria, sweating, and so forth. The irritation of the meninges is manifested by very violent pain of the neck with Kernig sign. At this time a lumbar puncture or a surgical intervention may be fatal. Therefore, one should not intervene during a bulbar crisis. Grave symptoms have occurred at the very beginning of anesthesia. They find it impossible to differentiate diagnostically, tumors of the fourth ventricle from endotheliomata of the recess, lateral bulbar gliomas, simple cerebellar bulbar cystic arachnoiditis, and so forth. Tumors of the hemispheres are often very slow in development. The cerebellar symptomatology appears early and this symptomatology remains for a long period unilateral. Also in the hemispheric tumors the vestibular attacks and a reflexia are very rare as are the tonic attacks which have only been reported in a single case of glioma of the hemisphere. In all other cases these attacks have been seen in lesions of the vermis or the pons. The pathologic findings in their cases are interesting but will not be abstracted here. Surgical intervention is recommended and a simple approach to the posterior fossa, using local anesthesia is recommended.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Dental Caries.—In studies of dental caries much attention has been given to the possible etiologic importance of certain aciduric bacteria. MORISHITA (*J. Bacter.*, 1929, **18**, 181) has found the presence of such organisms to be almost constant in the tooth enamel in the early stages, and also in the saliva of persons with carious teeth, but relatively rare

in those without dental caries. He found no definite proof, failing positive *in vivo* experiments, that they were directly responsible. The variation or pleomorphism found in the group makes it difficult to classify the bacteria found by others. The author, however, considers, because of the relatively high acidity produced, that these bacteria are probably associated in an intimate way with the disease.

Involvement of Medium-sized Arteries Associated with Syphilitic Aortitis.—SAPHIR (*Am. J. Path.*, 1929, **5**, 397) reports the results of a study of the proximal portions of the medium-sized arteries in 50 individuals presenting syphilitic aortitis. The object of the study was to find the early stages of syphilis in arteries which resembled the aorta structurally. For the purpose of this paper he grouped the innominate, carotid, subclavian and common iliac arteries as having an excess of elastic tissue and the superior mesenteric, inferior mesenteric, and femoral arteries as representing the muscular type of artery. The arteries of the elastic group were involved much more frequently than those of the muscular type. The majority of the lesions were found in the adventitia and in the intima. The changes in the adventitia consisted of endarteritis of the vasa vasorum and perivascular infiltration of lymphocytes and plasma cells. This lesion he interpreted as early syphilis. He was unable to determine whether the lesion primarily present was the endarteritis or the perivascular infiltration. The significant lesions of the intima were circumscribed button-like areas of fibrosis without degenerative changes. While these are not specific in character they were found most frequently at the site of syphilitic lesions in the adventitia. The media of the elastic type of arteries showed interruption of the continuity of the elastic fibers and fibrotic areas combined with circumscribed lymphocytic infiltrations. The media of the muscular type of arteries only rarely showed changes, which were confined to the outer portion of this coat where most of the elastic fibers are present.

The Rôle of Clasmatocytes in Protection Against Pneumococcus.—CLARK (*Arch. Path.*, 1929, **8**, 464) reports experiments on rabbits in which a mobilization of cells in the pleural cavity had been effected by the injection of aleuronat starch. Eighteen hours after this preparation, the cellular response is predominantly polymorphonuclear, while in a seventy-two-hour preparation the exudate is chiefly mononuclear, the pleural wall is thickened, filled with granulation tissue and many macrophages. The eighteen-hour preparation afforded no protection against a virulent strain of pneumococcus Type I injected into the pleural cavity nor against pneumococci that had been in contact with small amounts of antiserum. Seventy-two-hour preparation afforded no protection against pneumococci of the same strain, washed or unwashed; however, this preparation did confer marked protection against pneumococci that had been in contact with immune serum. The animals survived doses ten to a hundred times that which was fatal for normal rabbits on eighteen-hour preparations. It is concluded that there is a definite correlation between accumulation of clasmatocytes and resistance to pneumococcus infection in the pleural cavity of the rabbit.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Meningococcus Meningitis and Measures for Its Control.—McCoy (*United States Pub. Health Rep.*, 1929, **44**, 1595) refers to the exceptionally high prevalence of meningitis during the past year. The disease has been more prevalent in the West than in the East. Some cases have been fatal in as little as four hours, and the author reports a case fatal in twelve hours and another in twenty-five hours. It is pointed out that it is often not recognized that cases may occur without characteristic symptoms of the nervous system and that these cases may be established only by isolation of the organism from the blood stream or by its identification in skin lesions. Serologic types of the meningococcus are briefly discussed and it is pointed out that all types may prevail in the same epidemic and that they have no relation to clinical manifestations or to epidemiology. Clinical reports are cited to show that the serum available may usually be expected to give favorable results, though it is pointed out that the standardization of the preparation is on a most unsatisfactory basis. Under control measures the opinion of various authorities are noted and their conflicting nature emphasized. The control and disinfection of carriers are regarded as impracticable and it is pointed out that most carriers clear up in a few days regardless of what is done or is left undone. The writer closes with the following quotation from Rosenau: "It is not clear that any of the measures so far taken have either materially influenced the course of epidemics or prevented the spread of the disease."

A Study of Endemic Pellagra in Some Cotton Mill Villages of South Carolina.—Goldberger and his colleagues (*United States Pub. Health Rep.*, 1928, **43**, 2645) make the following observations on a group of 22,653 persons among whom 1147 cases of pellagra were observed, an incidence of 50.6 per 1000. Of the 4104 households among which that population was distributed, 18.5 per cent had at least one member affected by the disease in that year. Pellagra (in an endemic locality) is very much (two to six times) more prevalent than the experience of the physicians of the locality would seem to indicate. The fatality rate of the endemic disease, when definitely marked cases of all grades of severity are considered, would appear not to exceed 3 per cent. Striking peculiarities of age and sex distribution of the disease were observed. The observations of age incidence appear to indicate, what seems not to have been recognized heretofore, that endemic pellagra is prepon-

deratingly a disease of children of from two to fifteen years of age. Explanations of the peculiarities of age and of sex incidence are suggested. The single woman, as compared with the married, widowed, or divorced, is relatively exempt from the disease. In the population group under consideration, the single woman is usually a wage earner, which may place her in a somewhat more advantageous position with respect to diet than her married or widowed sister. The incidence of the disease was found to be markedly seasonal; 80 to 90 per cent of all cases had their "onset" within the period April to July, inclusive. One explanation suggested, in view of the proved dietary relation of the disease, is the variation in diet brought about by the seasonal modification of the food supply. The seasonal incidence of cases distinguished by their occurrence singly or otherwise in a household, and as initial and recurrent attacks, was studied. The disease was found to have a marked and very sharply limited season of prevalence the curve of which, with a slight lag, paralleled that of incidence. The study failed to disclose any consistent correlation between sanitary conditions and pellagra incidence. Such association as may at times be observed is regarded as accidental and to be explained by the intimate relation of the endemic disease to economic status, of which the sanitary condition may be an index. The study reveals the existence of a striking inverse correlation between the incidence of the endemic disease and family income. The continuous study of a selected village during a period of nearly six years appears to demonstrate that income shortage was a fundamental, though indirect, controlling factor in relation to the year-to-year fluctuation in the incidence of the disease. It is therefore inferred that the year-to-year fluctuations in the incidence of the endemic disease are bound up with fluctuations in economic conditions that influence the ability of a certain section of the population to procure an adequate diet. Marked seasonal variations in the food supply of a selected village are demonstrated. A relation of this variation in food supply to the striking seasonal incidence and prevalence of the disease is suggested.

Seasonal Variation of Diphtheria Antitoxin Content of the Blood of Adults and Adolescents.—PERKINS, HEEREN, MEGRAIL and GROSSMAN (*Am. J. Hyg.*, 1929, **10**, 13) have shown that a sample of school boys from eleven to fourteen years of age living and going to school in a crowded district has a definite picture showing low diphtheria antitoxin content in the late winter and in the spring, whereas a sample of adults whose occupation brings them into conditions of exposure not too dissimilar shows a totally different picture. No evidence has been found which might indicate that the normal autumn rise in diphtheria incidence is related to the antitoxin content of the blood of these individuals; the drop in incidence in late summer coincides with the general rise in antitoxin content in the series, but in view of the negative correlation at the time of increasing incidence it is at least questionable whether the recorded observations are significant. The work confirms Fitzgerald in demonstrating the existence of adults with practically no antitoxin in the blood and shows also that there may be a certain number of adolescents with similar characteristics. The authors believe that

additional studies of other groups will help to develop a picture of the cross section of antitoxin content of the general population, and even lead to appreciation of the part it plays in diphtheria incidence. They also state that it seems to them that this investigation strengthens the probability that the fundamental factor in seasonal variation in diphtheria is a modification of the resistance of the individual at the actual portal of entry.

The Schick Test in Palestine, a Country of Low Diphtheria Prevalence.—MANN and KLIGLER (*J. Prev. Med.*, 1929, **3**, 309) claim that diphtheria and scarlet fever are relatively far less prevalent in Palestine than in countries having a temperate climate. From about 3000 Schick tests it appears that the percentage of diphtheria immunes at the ages above eight years in Palestine is the same as found by Zingher in New York City, but that the immunization starts earlier among the Palestine children than in the New York children. A comparison of the native and foreign-born groups on the one hand, and the Ashkenazic and Sephardic communities on the other indicates that the native-born, especially in the Sephardic community, develop their diphtheria immunity much earlier than the foreign-born children. It would seem, therefore, that the absence of diphtheria in Palestine is only apparent. Since active immunity can probably be acquired only as the result of infection, the infection rate in the early age groups must be relatively high to produce so large a number of immunes.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF JANUARY 20, 1930.

Unusual Urinary and Blood Findings in a Myxedematous Dog.—DAVID L. DRABKIN and C. S. WAGGONER (from the Department of Physiological Chemistry, University of Pennsylvania). It seems of interest to report a number of unusual findings upon a dog which has been under observation since its birth, more than three years ago. The dog was born in the laboratory and has always lived in a metabolism cage. Except for a period of about two weeks, during its early puppyhood, it has been maintained exclusively on Cowgill's synthetic diet.[1] At the age of two months it was thyroidectomized, the upper pair of parathyroids being left intact. An exploratory operation six months later insured the completeness of thyroidectomy.

Shortly after the second operation the urine of this animal, collected in the usual fashion, was observed to turn black on standing. Preservation of the urine under toluene delayed the color change, but did not

[1] Cowgill, G.: J. Biol. Chem., 1923, **56**, 725.

prevent it. All the usual qualitative tests for homogentisic acid were positive. Very small amounts of crystals characteristic of the lead salt and dibenzoyl derivative of homogentisic acid have been obtained. The writers have not, however, succeeded in preparing from the urine sufficient amounts of pure homogentisic acid for analysis. For about one year the dog daily continued excreting urine which turned black on oxidation. During the past six months the phenomenon has become increasingly less constant and has been observed only occasionally.

Another finding, perhaps of even greater interest, was made by chance. For the past two years determinations of the "hemoglobin" by the acid hematin content (determined by Newcomer's method and spectrophotometrically) or by Stadie's cyanhemoglobin method have been found to be 8 to 15 per cent in excess of the hemoglobin, calculated from determinations of the oxygen capacity of the blood by the method of van Slyke or by determinations of oxyhemoglobin spectrophotometrically. An observation of this type is presumably rare, although recently somewhat similar observations have been made following splenectomy.[1]

Surface Properties of Chylomicrons.—R. L. NUGENT (from the Gladwyne Research Laboratory, Gladwyne, Pa.). General consideration lead to the hypothesis that chylomicrons in human blood serum are surrounded by films of serum protein. This hypothesis has been substantiated by two lines of experimental evidence involving the determination of the pH of the maximum isoelectric flocculation of chylomicrons in human serum and their behavior when gradually increasing amounts of protein precipitants are added to serum.

The probable importance of such protein films has been pointed out.

Double Chronaxie of the Nerve-muscle Complex.—W. A. H. RUSHTON (from the Physiological Laboratory, Cambridge University, and the Johnson Foundation, University of Pennsylvania). The temporal aspects of tissue excitation were discussed, with especial reference to the value of the chronaxie as a measure of them.

It was pointed out that the usual method of chronaxie measurement, namely, by the determination of only two threshold points, might give rise to serious errors where the tissue had more than one kind of excitable element present.

Experiments were then described affording strong evidence that in the normal frog's muscle there are two excitable substances with very different time relations.

1. The excised sartorius in equilibrium with the Ringer fluid through eighteen hours' immersion was excited for various durations by passing currents of various strengths in parallel lines through the whole fluid.

The nature of the strength-duration curves depended upon the angle between the muscle fibers and the direction of the current. The curve, in general, showed two components, one of chronaxie 0.3 sig., the other 7 sig., and the proportion in which these two entered could be varied at will by changing the angle.

[1] Stimson, B. B.: J. Biol. Chem. 1927, **81**, 62. Ray, G. B., and Isaac, L. A.: J. Biol. Chem., 1930, **85**, 549.

2. The same two curves could be obtained by stimulating a region not far from the pelvic end of the freshly excised muscle. When the cathode was toward the pelvic (nonneural) region the lower curve was more prominent; reversal of the current gave greater prominence to the other, which was also shown to have the same chronaxie as the nerve trunk directly excited.

3. A small strip of muscle with parallel fibers from the sternocutaneous of the bullfrog was excited at different angles and various durations. Analysis by polar coördinates showed there to be two excitable substances; the fibers of one lay in the same direction as those of the muscle, the other at right angles. The former had the long chronaxie, the latter the short.

To Summarize. The nerve-muscle complex contains two substances of widely differing chronaxie. The first has the same time relations as nerve (as Lapicque claims for muscle) but the fibers run at right angles to the muscle fibers. The second substance has a chronaxie over twenty times as long and lies in the same direction as the muscle fibers.

The Use of Thiocresol to Stimulate Wound Healing.—S. P. REIMANN (from the Research Institute of the Lankenau Hospital, Philadelphia). Since cell division is impossible unless sulphur is present in the nucleus in the −SH form, it is reasonable to suppose that the application of sulphydryl compounds will accelerate cell division. Healing of wounds is done by cell division. Of the many possible compounds, thioglucose was tried first. It stimulated healing but it also stimulated bacteria.

Thiocresol was then tried with the idea that the −SH part of the molecule would stimulate cell division and the cresol portion would tend to inhibit bacterial growth. These expectations were realized and thiocresol did accelerate wound healing. A number of practical points must be considered in the use for clinical purposes.

The main interest of the members of this Institute lies in the fact that cell division is stimulated by sulphydryl.

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